

(19) World Intellectual Property Organization  
International Bureau(43) International Publication Date  
20 June 2002 (20.06.2002)

PCT

(10) International Publication Number  
WO 02/48117 A1(51) International Patent Classification<sup>7</sup>: C07D 239/90,  
401/06, 471/04, 417/14, 401/14, 409/14, 403/06, A61K  
31/517, A61P 25/00

(21) International Application Number: PCT/JP01/10601

(22) International Filing Date: 5 December 2001 (05.12.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
PR2016 11 December 2000 (11.12.2000) AU

(71) Applicant (for all designated States except US): FUJISAWA PHARMACEUTICAL CO., LTD. [JP/JP]; 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(72) Inventors; and

(75) Inventors/Applicants (for US only): MATSUOKA, Nobuya [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). IWASHITA, Akinori [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). YAMAZAKI, Shunji [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). MIYAKE, Hiroshi [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). OHKUBO, Mitsuru [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). KAMIJO, Kazunori [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). NAKANISHI, Isao [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). HATTORI, Kouji [JP/JP]; c/o

Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). KIDO, Yoshiyuki [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). ISHIDA, Junya [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP). YAMAMOTO, Hirofumi [JP/JP]; c/o Fujisawa Pharmaceutical Co., Ltd., 4-7, Doshomachi 3-chome, Chuo-ku, Osaka-shi, Osaka 541-8514 (JP).

(74) Agent: TABUSHI, Eiji; c/o Fujisawa Pharmaceutical Co., Ltd., Osaka Factory, 1-6, Kashima 2-chome, Yodogawa-ku, Osaka-shi, Osaka 532-8514 (JP).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.

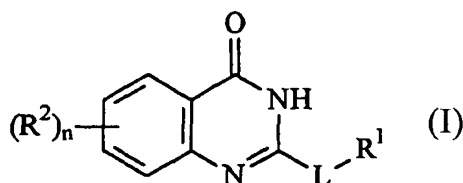
(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

**Published:**

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: QUINAZOLINONE DERIVATIVES

(57) Abstract: A quinazolinone derivatives having poly(adenosine 5'-diphospho-ribose)polymerase (PARP) inhibitory activity represented by the formula (I), wherein R<sup>1</sup> is optionally substituted cyclic amino groups or optionally substituted amino group, R<sup>2</sup> is substituent, n means an integer from 0 to 4, and L is lower alkylene or lower alkenylene, or its prodrug, or their salts.

## DESCRIPTION

## QUINAZOLINONE DERIVATIVES

5 Technical Field

This invention relates to novel quinazolinone derivatives having pharmacological activity, to a process for their production and to a pharmaceutical composition containing the same.

10 Background Art

Poly(adenosine 5'-diphospho-ribose)polymerase ["poly(ADP-ribose)polymerase" or "PARP", which is also sometimes called "PARS" for "poly(ADP-ribose)synthetase"] is an enzyme located in the nuclei of cells of various organs, including muscle, heart and brain cells. PARP plays a physiological role in the repair of strand breaks in DNA. Once  
15 activated by damaged DNA fragments, PARP catalyzes the attachment of up to 100 ADP-ribose units to a variety of nuclear proteins, including histones and PARP itself.

Some quinazolinone derivatives having inhibitory activity of PARP have been known, for example, in WO95/24379, WO98/33802 and WO99/11624.

20 Disclosure of the Invention

This invention relates to novel quinazolinone compounds, which have pharmaceutical activity such as PARP inhibiting activity, to a process for their production, to a pharmaceutical composition containing the same and to a use thereof.

One object of this invention is to provide the novel quinazolinone compounds,  
25 which have a PARP inhibiting activity.

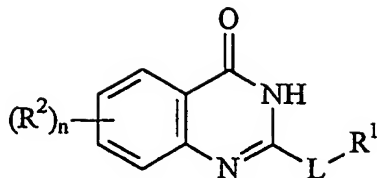
Another object of this invention is to provide a process for production of the quinazolinone compounds.

A further object of this invention is to provide a pharmaceutical composition containing the quinazolinone compound as an active ingredient.

30 Still further object of this invention is to provide a use of the quinazolinone compound for manufacturing a medicament for treating or preventing various diseases, or a method of treating or preventing various diseases by administering the quinazolinone compound in an effective amount to inhibit PARP activity.

Thus, the present invention provides the following.

35 [1] A compound of the formula:



5

wherein  $R^1$  is optionally substituted cyclic amino groups or optionally substituted amino group,

$R^2$  is substituent,

$n$  means an integer from 0 to 4, and

10

$L$  is lower alkylene or lower alkenylene,

or its prodrug, or their salts.

[2] The compound according to [1], wherein

$R^2$  is halogen, nitro, amino, acylamino, aryl(lower)alkylamino, lower alkylamino, lower alkyl, lower alkynyl, lower alkoxy, acyl, or cyclic amino group optionally substituted with lower alkyl.

15

[3] The compound according to [2], wherein

$R^1$  is (1) cyclic amino group optionally substituted with one or more substituent(s) selected from the group consisting of halogen, cyano, hydroxy, amino, oxo, lower alkyl, lower alkenyl, lower alkynyl, aryl(lower)alkyl, aryl(lower)alkynyl, acyl, lower alkylsulfonyl, optionally substituted heteroaryl and optionally substituted aryl, or (2) amino optionally substituted with 1 or 2 substituent(s) selected from the group consisting of lower alkyl, aryl, heteroaryl(lower)alkyl, aryl(lower)alkoxycarbonyl and aryl(lower)alkyl optionally substituted with aryl or aryloxy.

20

[4] The compound according to [3], wherein

$R^1$  is cyclic amino group optionally substituted with optionally substituted heteroaryl or optionally substituted aryl.

25

[5] The compound according to [4], wherein

$R^1$  is cyclic amino group with saturated or unsaturated monocyclic group with one or more nitrogen atom(s), which is substituted with optionally substituted heteroaryl or optionally substituted aryl.

30

[6] The compound according to [5], wherein

$R^1$  is tetrahydropyridyl, piperidyl or piperazinyl, each of which is substituted with optionally substituted heteroaryl or optionally substituted aryl.

[7] The compound according to any one of [4], [5] and [6], wherein

substituent(s) of optionally substituted heteroaryl is lower alkyl, halogen, cyano or acyl, or

35

substituent(s) of optionally substituted aryl is halogen, cyano, hydroxy, carboxy, nitro, amino, lower alkyl, hydroxy(lower)alkyl, lower alkoxy, lower alkyl thio, halo(lower)alkyl, lower alkylamino, acylamino, halo(lower)alkoxy, aryl, aryloxy, or acyl.

5 [8] The compound according to [3], wherein

R<sup>1</sup> is cyclic amino groups with saturated and unsaturated fused cyclic groups, which is substituted with optionally substituted lower alkyl.

[9] The compound according to any one of [4], [5], [6], [7] and [8], wherein  
L is trimethylene.

10 [10] The compound according to [9], which is selected from the group consisting of:

(1) 5-chloro-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-  
4(3H)-quinazolinone,

(2) 2-{3-[4-(4-hydroxyphenyl)-3,6-dihydropyridin-1(2H)-yl]propyl}-  
4(3H)-quinazolinone,

15 (3) 8-methyl-2-{3-[4-(4-methoxyphenyl)-3,6-dihydro-1(2H)-pyridinyl]propyl}-  
4(3H)-quinazolinone,

(4) 8-chloro-2-{3-[4-(4-fluorophenyl)-3,6-dihydro-1(2H)-pyridinyl]propyl}-  
4(3H)-quinazolinone,

20 (5) 8-chloro-2-{(1E)-3-[4-(4-fluorophenyl)-3,6-dihydro-1(2H)-pyridinyl]-1-propenyl}-  
4(3H)-quinazolinone,

(6) 8-Chloro-2-[[4-(4-pyridinyl)-3,6-dihydro-1(2H)-pyridinyl] propyl]-  
4(3H)-quinazolinone,

(7) 2-{3-[4-(4-chlorophenyl)-1-piperazinyl]propyl}-4(3H)-quinazolinone,

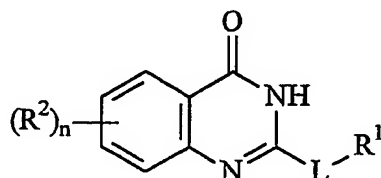
(8) 2-{3-[4-(4-pyridyl)-1-piperazinyl]propyl}-4(3H)-quinazolinone,

25 (9) 2-[3-(1,4,5,6-Tetrahydrobenzo[f]isoquinolin-3(2H)-yl)propyl]-  
4(3H)-quinazolinone, and

(10) 8-methyl-2-[3-(1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)propyl]-  
4(3H)-quinazolinone.

[11] A process for preparing a compound of the formula:

30



35

wherein R<sup>1</sup> is optionally substituted cyclic amino groups or optionally substituted



amino group,

$R^2$  is substituent,

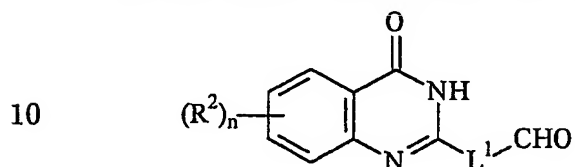
$n$  means an integer from 0 to 4, and

$L$  is lower alkylene or lower alkenylene,

5 or its prodrug, or their salts,

which comprises,

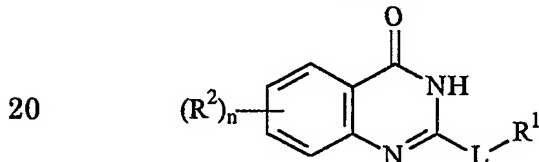
(1) reacting the formyl group of the compound (II) of the formula:



or its amination derivative, or their salt, and imino group of the compound (IV) of the formula:



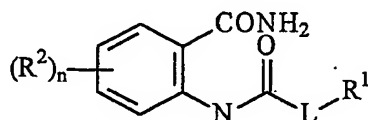
or its salt, in the presence of a reducing agent to provide a compound of the formula:



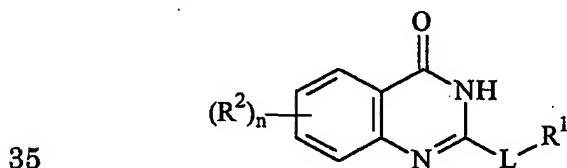
or its salt, in the above formulae,

$R^1$ ,  $R^2$ ,  $n$  and  $L$  are each as defined above, and  $L^1$  is lower alkylene or lower alkenylene delating a methylene group from the end of the one defined in  $L$ , or

25 (2) subjecting the compound (III) of the following formula:



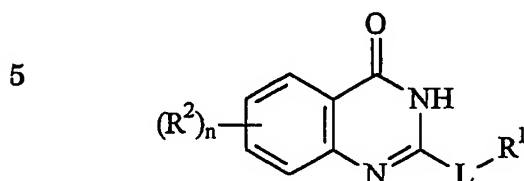
30 or its salt, to cyclization reaction in the presence of base to provide a compound of the formula:



or its salt, in the above formulae,

$R^1$ ,  $R^2$ ,  $n$  and  $L$  are each as defined above.

[12] A pharmaceutically composition comprising a compound of the formula:



wherein  $R^1$  is optionally substituted cyclic amino groups or optionally substituted amino group,

$R^2$  is substituent,

$n$  means an integer from 0 to 4, and

$L$  is lower alkylene or lower alkenylene,

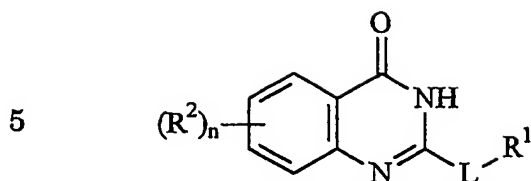
or its prodrug, or their pharmaceutically acceptable salts, and a pharmaceutically acceptable carrier, wherein said compound is present in an amount effective for inhibiting PARP activity.

[13] The pharmaceutical composition of [12] for treating or preventing diseases ascribed by NMDA- and NO-induced toxicity.

[14] The pharmaceutical composition of [12] for extending the lifespan or proliferative capacity of cells or altering gene expression of senescent cells

[15] The pharmaceutical composition of [13] for treating or preventing tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke; Alzheimer's disease; Parkinson's disease; epilepsy; Amyotrophic Lateral Sclerosis (ALS); Huntington's disease; schizophrenia; chronic pain; ischemia and loss following hypoxia; hypoglycemia; ischemia; trauma; nervous insult; previously ischemic heart or skeletal muscle tissue; radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy; skin aging; atherosclerosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescence diseases; inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and tumor.

[16] A method of inhibiting PARP activity comprising administering a compound of the formula:



wherein  $R^1$  is optionally substituted cyclic amino groups or optionally substituted amino group,

$R^2$  is substituent,

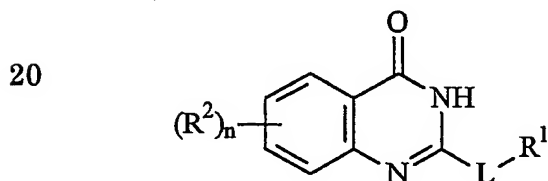
10  $n$  means an integer from 0 to 4, and

$L$  is lower alkylene or lower alkenylene,

or its prodrug, or their pharmaceutically acceptable salts, and a pharmaceutically acceptable carrier, wherein said compound is present in an amount effective for inhibiting PARP activity.

15

The quinazolinone compounds of this invention can be represented by the following formula (I):



[wherein  $R^1$  is optionally substituted cyclic amino groups or optionally substituted amino group,  $R^2$  is substituent,  $n$  means an integer from 0 to 4, and  $L$  is lower alkylene or lower alkenylene.] or its prodrug, or their salt.

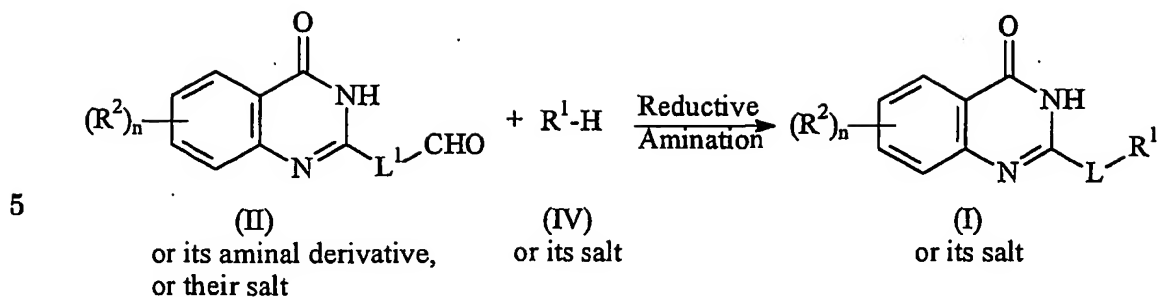
25

The compound (I) or its prodrug, or their salt can be prepared by the following processes. In the following formulae, compounds may be prodrugs or their salts.

30

#### Process 1

35



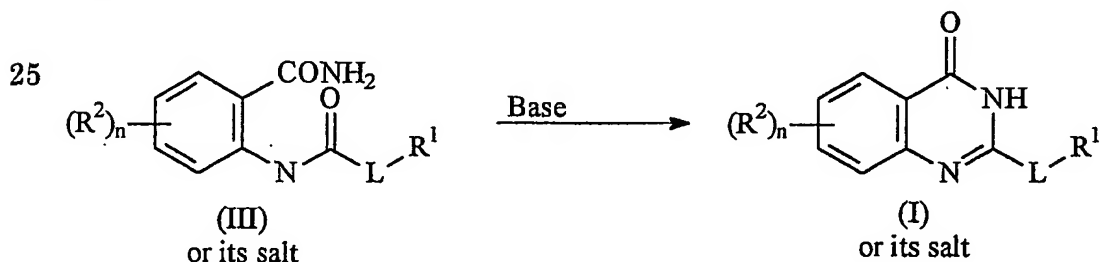
[wherein,  $\text{R}^1$ ,  $\text{R}^2$ ,  $n$  and  $\text{L}$  are each as defined above, and  $\text{L}^1$  is lower alkylene or lower alkenylene delating a methylene group from the end of the lower alkylene defined in  $\text{L}$ ]

10 In this process the compound (I) can be produced by reacting the formyl group of the compound (II) and imino or amino group of the compound (IV) in the presence of a reducing agent such as sodium cyanoborohydride, sodium borohydride, lithium cyanoborohydride, borane, diethylsilane, catalytic reduction with Raney nickel, or the like. This reaction preferably carried out in the acidic condition, such as the presence of acid  
15 (e.g., acetic acid, hydrogen chloride, trifluoroacetic acid).

The reaction is usually carried out in a conventional solvent such as water, an alcohol (e.g., methanol, ethanol or isopropyl alcohol), ether (e.g., tetrahydrofuran, dioxane, diethylether), amide (e.g., N,N-dimethylformamide, N,N-dimethylacetamide), nitrile (e.g., acetonitrile), or any other organic solvent which does not adversely affect the reaction.

20 The reaction may be usually carried out under cooling to heating since the reaction temperature is not critical.

### Process 2



30 [wherein,  $\text{R}^1$ ,  $\text{R}^2$ ,  $n$  and  $\text{L}$  are each as defined above.]

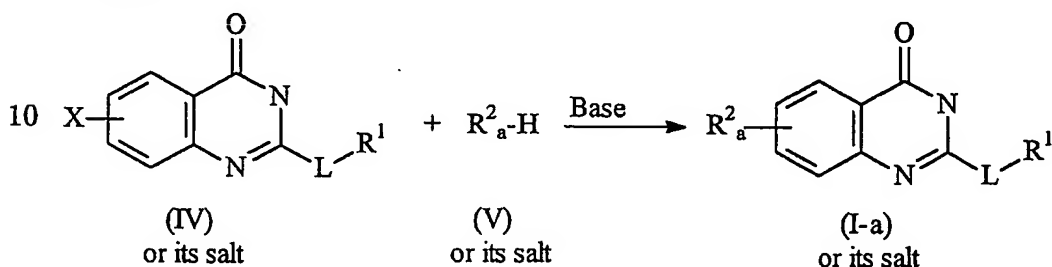
In this process, the compound (I) can be produced by subjecting the compound (III) to cyclization reaction in the presence of base, such as inorganic bases, for example, an alkali metal [e.g., sodium or potassium], alkoxide, hydroxide, carbonate or bicarbonate thereof, or organic bases such as a trialkylamine [e.g., trimethylamine or triethylamine] or  
35 the like.

The reaction is usually carried out in a conventional solvent such as water, an

alcohol (e.g., methanol, ethanol or isopropyl alcohol), ether (e.g., tetrahydrofuran, dioxane, diethylether), amide (e.g., N,N-dimethylformamide, N,N-dimethylacetamide), nitrile (e.g., acetonitrile), or any other organic solvent which does not adversely affect the reaction.

The reaction may be usually carried out under cooling to heating since the reaction  
5 temperature is not critical.

### Process 3

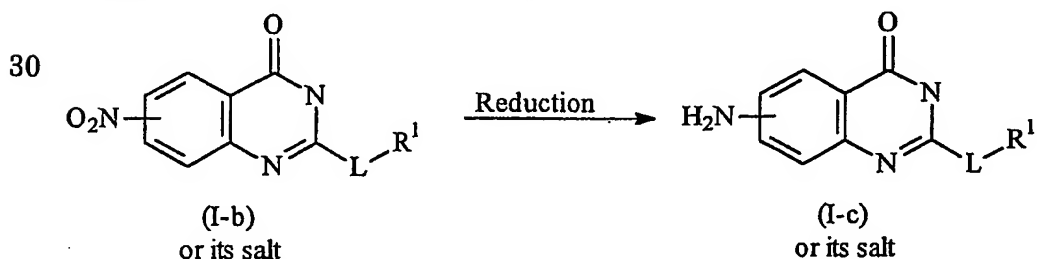


[wherein, X is leaving group, R²ₐ is cyclic amino group, R¹, n and L are each as defined  
15 above.]

In this process, the compound (I-a) or its salts can be produced by reacting the compound (IV) or its salt and compound (V) in the presence of base, such as inorganic bases, for example, an alkali metal [e.g., sodium or potassium], alkoxide, hydroxide, carbonate or bicarbonate thereof, or organic bases such as a trialkylamine [e.g.,  
20 trimethylamine or triethylamine] or the like.

The reaction is usually carried out in a conventional solvent such as an alcohol (e.g., methanol, ethanol or isopropyl alcohol), ether (e.g., tetrahydrofuran, dioxane, diethylether), amide (e.g., N,N-dimethylformamide, N,N-dimethylacetamide), nitrile (e.g., acetonitrile), or any other organic solvent which does not adversely affect the reaction.  
25 The reaction may be usually carried out under cooling to heating since the reaction temperature is not critical.

### Process 4



35 [wherein, R¹, n and L are each as defined above.]

In process 4, the compound (I-c) or its salt can be prepared by subjecting a

compound (I-b) or its salt to reduction.

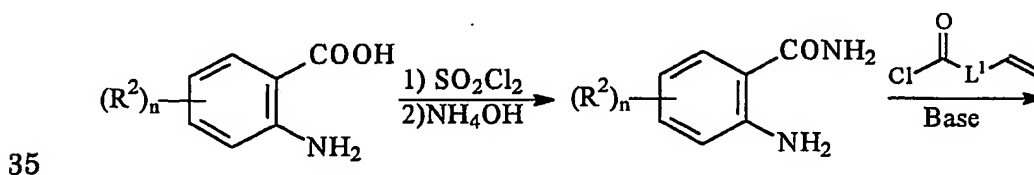
The reduction is carried out by chemical reduction, catalytic reduction, or the like. Suitable reducing agents to be used in chemical reduction are a combination of metal [e.g. tin, zinc, iron, etc.] or metallic compound [e.g. chromium chloride, chromium acetate, etc.] and an organic or inorganic acid [e.g. formic acid, acetic acid, propionic acid, trifluoroacetic acid, p-toluenesulfonic acid, hydrochloric acid, hydrobromic acid, etc.]. Suitable catalysts to be used in catalytic reduction are conventional ones such as platinum catalyst [e.g. platinum, platinum black, platinum oxide, etc.], palladium catalyst [e.g. palladium black, palladium oxide, palladium on carbon, etc.], nickel catalyst [e.g. reduced nickel, nickel oxide, Raney nickel, etc.], or the like.

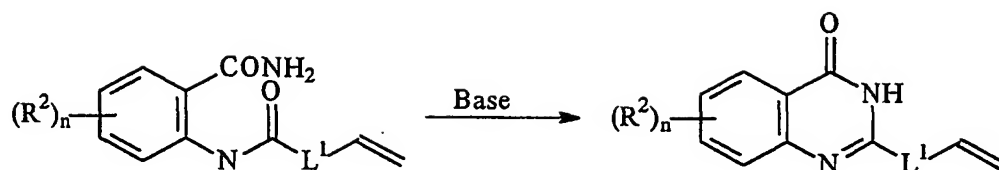
The reduction is usually carried out in a conventional solvent which does not adversely influence the reaction such as water, an alcohol [e.g. methanol, ethanol, propanol, etc.], N,N-dimethylformamide, or a mixture thereof. Additionally, in case that the above-mentioned acids to be used in chemical reduction are in liquid, they can also be used as a solvent. The reaction temperature of this reduction is not critical and the reaction is usually carried out under cooling to warming.

The compound of the present invention can be purified by any conventional purification methods employed for purifying organic compounds, such as recrystallization, column chromatography, thin-layer chromatography, high-performance liquid chromatography and the like. The compounds can be identified by conventional methods such as NMR spectrography, mass spectrography, IR spectrography, elemental analysis, and measurement of melting point.

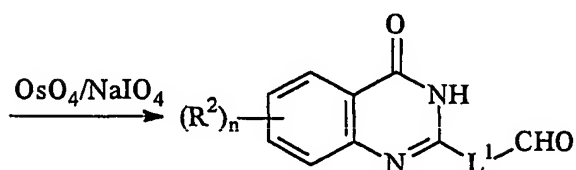
Some of the starting compounds (II) or (III) are novel and can be prepared by the well-known processes or its analogous processes, for example, the processes described in the J. Med. Chem. 1998, 41, 5247-5256 and J. Org. Chem., 21, 478- (1956). The following processes are given as an example.

### Reference Process 1

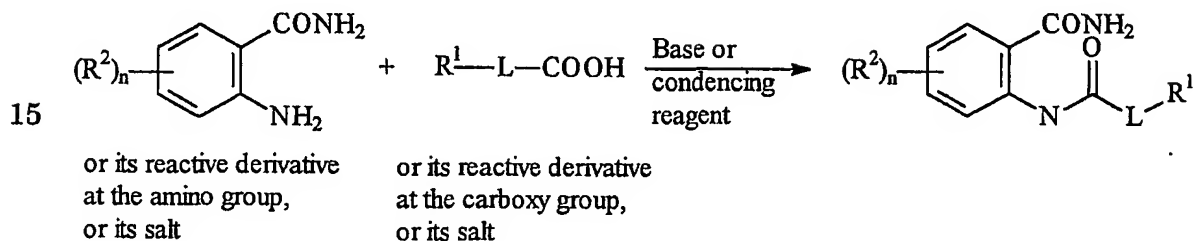




5



10

Reference Process 2

15

[wherein, R<sup>1</sup>, R<sup>2</sup>, n, L and L<sup>1</sup> are each as defined above.]

20

Suitable salts of the compounds of the present invention are pharmaceutically acceptable conventional non-toxic salts and can be an organic acid addition salt (e.g. formate, acetate, trifluoroacetate, maleate, tartarate, oxalate, methanesulfonate, benzenesulfonate, toluenesulfonate, etc.), an inorganic acid addition salt (e.g. hydrochloride, hydrobromide, sulfate, phosphate, etc.), a salt with an amino acid (e.g. aspartic acid salt, glutamic acid salt, etc.), or the like.

The "prodrug" means the derivatives of compounds of the present invention having a chemically or metabolically degradable group, which becomes pharmaceutically active after biotransformation.

The compounds of formula (I) may contain one or more asymmetric centers and thus they can exist as enantiomers or diastereoisomers. Furthermore certain compounds of formula (I) which contain alkenyl groups may exist as cis- or trans-isomers. In each instance, the invention includes both mixtures and separate individual isomers.

The compounds of the formula (I) may also exist in tautomeric forms and the invention includes both mixtures and separate individual tautomers.

The compound of the formula (I) and its salt can be in a form of a solvate, which is

included within the scope of the present invention. The solvate preferably include a hydrate and an ethanolate.

Also included in the scope of invention are radiolabelled derivatives of compounds of formula (I) which are suitable for biological studies.

5

In the above and subsequent description of the present specification, suitable examples and illustrations of the various definitions, which the present invention includes within the scope thereof, are explained in detail as follows.

The term "lower" means a group having 1 to 6 carbon atom(s), unless otherwise  
10 provided.

Suitable "lower alkyl" and lower alkyl moiety in the terms "hydroxy(lower)alkyl", "lower alkylsulfonyl", "lower alkylthio" and "heteroaryl(lower)alkyl" include a straight or branched alkyl having 1 to 6, in particular 1 to 2, carbon atoms. Preferable examples which may be mentioned are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl,  
15 pentyl and hexyl.

Preferable example which may be mentioned as "hydroxy(lower)alkyl" is hydroxymethyl. Preferable examples which may be mentioned as "lower alkylsulfonyl" are methylsulfonyl and ethylsulfonyl. Preferable examples which may be mentioned as "lower alkylthio" are methylthio and ethylthio.

20 Suitable "lower alkenyl" includes a straight or branched alkenyl having 2 to 6 carbon atoms. Preferable examples which may be mentioned are ethenyl(vinyl), propenyl (i.e., allyl or 1-propenyl), butenyl and isobutenyl.

Suitable "lower alkynyl" and lower alkynyl moiety in the term "aryl(lower)alkynyl" include a straight or branch alkynyl having 2 to 6 carbon atoms.

25 Preferable examples which may be mentioned are ethynyl and propynyl.

Preferable example which may be mentioned as "aryl(lower)alkynyl" is phenylethynyl.

Suitable "lower alkylene" includes a straight or branched alkylene having 1 to 6, in particular 3, carbon atoms. Preferable examples which may be mentioned are methylene,  
30 ethylene, trimethylene, propylene, methyltrimethylene (1- or 2- methyltrimethylene) and hexamethylene, preferably trimethylene.

Suitable "lower alkenylene" includes a straight or branched alkenylene having 1 to 6, in particular 3, carbon atoms. Preferable examples which may be mentioned are vinylene, propenylene, dimethylpropenylene (e.g., 3,3-dimethylpropenylene, etc.) and  
35 hexenylene preferably propenylene.

Suitable "lower alkoxy" and lower alkoxy moiety in the term



“aryl(lower)alkoxycarbonyl” includes straight or branched alkoxy having 1 to 6, in particular 1 to 2, carbon atoms. Preferable examples which may be mentioned are methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy and tert-butoxy, preferably methoxy. Suitable “lower alkylamino” and lower alkylamino moiety in the term

5 “aryl(lower)alkylamino” include mono(lower)alkylamino and di(lower)alkylamino.

Preferable examples which may be mentioned are methylamino, dimethylamino, ethylamino, dimethylamino, n-propylamino, isopropylamino, n-butylamino, iso-butylamino, sec-butylamino and tert-butylamino, preferably dimethylamino and diethylamino.

Suitable “aryl” and aryl moiety in the terms “aryloxy”, “aryl(lower)alkynyl”,  
10 “aryl(lower)alkylamino” and “aryl(lower)alkoxycarbonyl” may be intended to mean a mono-, di- or polynuclear aromatic radical having preferably 6 to 12 carbon atoms, such as phenyl, naphthyl, tetrahydronaphthyl, indenyl, indanyl (1,2-dihydroindenyl), fluorenyl and the like, preferably phenyl or naphthyl.

Preferable examples which may be mentioned as “aryloxy” are phenoxy and  
15 naphtyloxy.

Preferable example which may be mentioned as “aryl(lower)alkoxycarbonyl” is benzyloxycarbonyl.

Suitable “aryl(lower)alkyl” and aryl(lower)alkyl moiety in the term  
“aryl(lower)alkylamino” means arylalkyl which has preferably 6 or 10 carbon atoms in the  
20 aryl part (preferably phenyl or naphthyl, in particular phenyl) and preferably 1 to 6, in particular 1 to 4, carbon atoms in the alkyl part, it being possible for the alkyl part to be straight-chain or branched. Benzyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl and naphthylmethyl may be mentioned as examples and as preferred.

Preferable examples which mentioned as “aryl(lower)alkylamino” are  
25 benzylamino and phenethylamino.

Suitable “acyl” and acyl moiety in the “acylamino” may be aliphatic acyl, aromatic acyl, aliphatic acyl optionally substituted aryl or heteroaromatic acyl, which are derived from carboxylic acid.

The aliphatic acyl may include

30 (1) lower alkanoyl optionally substituted with one or more suitable substituent(s) such as hydroxy, lower alkoxy, carboxy, protected carboxy, halogen, lower alkylthio, heterocyclicthio, oxo, cyclo(lower)alkyl or a heterocyclic group (e.g. formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, hexanoyl, 3,3-dimethylbutanoyl, 3-hydroxy-3-methylbutanoyl, 3-oxo-butanoyl, 3-methoxycarbonylpropanoyl,  
35 3-carboxypropanoyl, 4-methoxycarbonylbutanoyl, 4-carboxybutanoyl, methylthioacetyl, (1-methylimidazol-2-yl)thioacetyl, hydroxyacetyl, methoxyacetyl, ethoxyacetyl,

3-methoxybutanoyl, chloroacetyl, morpholinoacetyl, piperidinylacetyl, 4-methylpiperidin-1-ylacetyl, 4-hydroxypiperidinyl, pyrrolidinylacetyl, 4-(pyrimidin-2-yl)piperidinylacetyl, 3-hydroxypyrrolidinylacetyl, oxolan-4-ylacetyl, and so on);

5 (2) cyclo(lower)alkanecarbonyl (e.g. cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, and so on);

(3) lower alkenoyl (e.g. acryloyl, methacryloyl, crotonoyl, 3-methylbutanoyl, and so on);

The aromatic acyl may include aroyl optionally substituted with one or more suitable substituent(s) such as nitro (e.g. benzoyl, naphthoyl, nitrobenzoyl, and so on), or  
10 the like.

The aliphatic acyl substituted with aryl may include ar(lower)alkanoyl which may have one or more suitable substituent(s) such as lower alkoxy (e.g. phenylacetyl, 4-methoxyphenylacetyl, and so on) or the like.

The heteroaromatic acyl is a carbonyl group to which is binded to heteroaryl, such  
15 as furylcarbonyl or the like.

The term "halogen" means fluoro, chloro, bromo or iodo.

Suitable "halo(lower)alkyl" and halo(lower)alkyl moiety in the term "halo(lower)alkoxy" contains 1 to 4, in particular 1 or 2, carbon atoms, and preferably 1 to 9, in particular 1 to 5, identical or different halogen atoms, preferably fluorine, chlorine and  
20 bromine, in particular fluorine and chlorine. Examples which may be mentioned are trifluoromethyl, trichloromethyl, chlorodifluoromethyl, dichlorofluoromethyl, chloromethyl, bromomethyl, 1-fluoroethyl, 2-fluoroethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl and pentafluoroethyl, preferably trifluoromethyl.

Suitable "heteroaryl" and heteroaryl moiety in the terms "heteroaryl(lower)alkyl" and "heteroaromatic acyl" is intended to mean 5- to 7-membered rings having preferably 1  
25 to 3, in particular 1 or 2, identical or different heteroatoms. Heteroatoms in the heteroaryl are oxygen, sulfur or nitrogen. Examples which may be mentioned are furyl, thienyl, pyrazolyl, imidazolyl, triazolyl (e.g., 1,2,3- and 1,2,4-triazolyl, etc.), isoxazolyl, thiazolyl, isothiazolyl, oxadiazolyl (e.g., 1,3,4-, and 1,2,5-oxadiazolyl, etc.), azepinyl, pyrrolyl,  
30 pyridinyl, piperazinyl, pyridazinyl, pyrimidinyl, pyrazinyl, triazinyl (e.g., 1,3,5-, 1,2,4- and 1,2,3-triazinyl, etc.), oxazinyl (e.g., 1,2,4- and 1,2,6-oxazinyl, etc.), oxepinyl, thiepinyl and diazepinyl (e.g., 1,2,4-diazepinyl, etc.), preferably thienyl, pyrazolyl, imidazolyl, thiazolyl, pyridinyl and pyrazinyl.

Suitable "cyclic amino group" are heteroaromatic or aliphatic ring systems having  
35 one or more nitrogen atoms as the heteroatom, in which the heterocyclic rings can be saturated or unsaturated, can be one ring system or several fused ring systems, and

optionally contain further heteroatoms, such as nitrogen, oxygen and sulfur and the like.

Cyclic amino groups can furthermore also denote a spiro ring or a bridged ring system. The number of atoms which form cyclic amino groups is not limited, for example in the case of a single-ring system, they comprise 3 to 8 atoms, and in the case of a three-ring system,

5 they comprise 7 to 11 atoms.

Preferable examples of "cyclic amino group" are described as follows:

- (1) examples which may be mentioned of cyclic amino group with saturated monocyclic groups with one or more nitrogen atom(s) as the heteroatom are azetidiny (3-azetidiny), pyrrolidiny (e.g., 1- and 3-pyrrolidiny, etc.), piperidyl (e.g., 1- and 4-piperidyl, etc.),  
 10 homopiperidino (e.g., hexahydro-1H-azepin-1-yl, etc.), homopiperaziny (e.g., hexahydro-1H-1,4-diazepin-1-yl, etc.), imidazolidiny (e.g., 1-imidazolidiny, etc.), piperaziny (e.g., 1-piperaziny, etc.), perhydropyrimidiny (e.g., perhydropyrimidin-1-yl, etc.) and diazacycloheptany (e.g., 1,4-diazacycloheptan-1-yl, etc.);
- (2) examples which may be mentioned of cyclic amino group with unsaturated  
 15 monocyclic groups with one or more nitrogen atom(s) as the heteroatom are pyrroliny (e.g., 2-pyrrolin-1-yl, etc.), pyrroly (e.g., 1-pyrroly, etc), tetrahydropyridiny (e.g., 3,6-dihydro-1(2H)-pyridiny, etc.), pyridiny (e.g., 2-pyridiny, etc.), tetrahydroazepiny (e.g., 2,3,6,7-tetrahydro-1H-azepin-1-yl, 2,3,4,7-tetrahydro-1H-azepin-1-yl, etc.), imidazolyl (1-imidazolyl), pyrazolyl, triazolyl, tetrazolyl, tetrazolyl, pyrimidiny, pyraziny,  
 20 pyridaziny, dihydro-pyridaziny (e.g., 1,2-dihydro-pyridazin-1-yl, etc.) and dihydro-pyrimidiny (e.g., 1,2-dihydro-pyrimidin-1-yl, etc.);
- (3) examples which may be mentioned of cyclic amino groups with saturated and unsaturated monocyclic groups with one to three nitrogen atoms and one to two sulfur atoms as heteroatoms are thiazolidiny (e.g., 3-thiazolidiny, etc.), isothiazoliny (e.g.,  
 25 2-isothiazoliny, etc.) and thiomorpholino;
- (4) examples which may be mentioned of cyclic amino groups with saturated and unsaturated monocyclic groups with one to three nitrogen atoms and one to two oxygen atoms as heteroatoms are oxazolyl, isoxazolyl, oxadiazolyl (e.g., 1,2,4-oxadiazolyl, and 1,3,4-oxadiazolyl) or morpholiny;
- (5) examples which may be mentioned of cyclic amino groups with saturated and unsaturated fused cyclic groups are indolyl (e.g., 1-indolyl, etc.), dihydrobenzimidazolyl (e.g., 1,2-dihydrobenzimidazol-1-yl, etc.), perhydropyrrolo[1,2-a]pyraziny (e.g., perhydropyrrolo[1,2-a]pyrazin-2-yl, etc.), tetrahydrobenzo[f]isoquinoliny (e.g., 1,4,5,6-tetrahydrobenzo[f]isoquinolin-3(2H)-yl, etc.), hexahydrobenz[f]isoquinoliny (e.g.,  
 35 cis- and trans-1,4,4a,5,6,10b-hexahydrobenz[f]isoquinolin-3(2H)-yl, etc.), tetrahydropyrido[3,4-b]indolyl (e.g., 1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl, etc.)

tetrahydrobenzazepinyl (e.g., 1,2,4,5-tetrahydro-3H-benzazepin-3-yl, etc.)

dihydroisoquinolinyl (e.g., 3,4-dihydro-2(1H)-isoquinolinyl, etc.);

(6) examples which may be mentioned of cyclic amino groups with spirocyclic groups are azaspiro[4,5]decanyl (e.g., 2-azaspiro[4,5]decan-2-yl, etc.),

5 spiro[1H-indene-1,4'-piperidinyl] (e.g., spiro[1H-indene-1,4'-piperidin-1'-yl], etc.), and dihydrospiro[1H-indene-1,4'-piperidinyl] (e.g., 2,3-dihydrospiro[1H-indene-1,4'-piperidin-1'-yl], etc.);

(7) examples which may be mentioned of cyclic amino groups bridged heterocyclic groups are azabicyclo[2,2,1]heptanyl (e.g., 2-azabicyclo[2,2,1]heptan-7-yl, etc.) and

10 diazabicyclo[2.2.1]heptyl (e.g., 2,5-diazabicyclo[2.2.1]hept-2-yl, etc.).

Among the above, preferable "cyclic amino group" included in R1 is above-mentioned (1) or (2), in which the most preferable one is piperidinyl, tetrahydropyridinyl and piperazinyl.

15 It has been known that, during major cellular stresses, the activation of PARP can rapidly lead to cell damage or death through depletion of energy stores and PARP activation play a key role in both NMDA- and NO-induced neurotoxicity (Zhang et. al., Science, 263: 687-89 (1994)). Therefore, the compound possessing PARP inhibiting activity, such as the compound (I) of this invention, or pharmaceutically acceptable salts are useful in treating  
20 and preventing various diseases ascribed by NMDA- and NO-induced toxicity. Such diseases include, for example, tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke; Alzheimer's disease; Parkinson's disease; epilepsy; amyotrophic lateral  
25 sclerosis (ALS); Huntington's disease; schizophrenia; chronic pain; ischemia and neuronal loss following hypoxia; hypoglycemia; ischemia; trauma; and nervous insult.

It has been demonstrated that PARP inhibitor are useful in deducing infarct size (Thiemermann et al, Proc. Natl. Acad. Sci. USA, 94: 679-83 (1997)). Therefore, the compound possessing PARP inhibiting activity, such as the compound (I) of this invention,  
30 or pharmaceutically acceptable salts are useful in treatment and prevention of previously ischemic heart or skeleton muscle tissue.

It is also known that PARP is thought to play a role in enhancing DNA repair. So, the compound possessing PARP inhibiting activity, such as the compound (I) of this invention, or pharmaceutically acceptable salts are effective in treating and preventing  
35 radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy.

Further, the compound possessing PARP inhibiting activity, such as the compound (I) of this invention, or pharmaceutically acceptable salts are useful in extending the life-span and proliferative capacity of cells and altering gene expression of senescent cells. They are useful for treating and preventing skin aging; Alzheimer's diseases;

5 atherosclerosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescence diseases.

Still further, the compound possessing PARP inhibiting activity, such as the compound (I) of this invention, or pharmaceutically acceptable salts are effective in treating  
10 and preventing inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and tumor. Also, they are useful in reducing proliferation of tumor cells and making synergistic effect when tumor cells are co-treated with an alkylating drug.

The compound possessing PARP inhibiting activity, such as the compound (I) of this invention, or pharmaceutically acceptable salts are effective in treating and preventing  
15 pituitary apoplexy; conjunctivitis; retinoblastoma; retinopathy; acute retinal necrosis syndrome; Sjogren's syndrome.

The compound (I), its prodrug, or their salt can be administered alone or in the form of a mixture, preferably, with a pharmaceutical vehicle or carrier.

The active ingredient of this invention can be used in the form of a pharmaceutical  
20 preparation, for example, in solid, semisolid or liquid form, which contains a compound (I), as an active ingredient, in admixture with an organic or inorganic carrier or excipient suitable for external (topical), enteral, intravenous, intramuscular, parenteral or intramucous applications. The active ingredient can be formulated, for example, with the conventional non-toxic, pharmaceutically acceptable carriers for ointment, cream, plaster, tablets, pellets,  
25 capsules, suppositories, solution (saline, for example), emulsion, suspension (olive oil, for example), aerosols, pills, powders, syrups, injections, troches, cataplasms, aromatic waters, lotions, buccal tablets, sublingual tablets, nasal drops and any other form suitable for use. The carriers which can be used are water, wax, glucose, lactose, gum acacia, gelatin, mannitol, starch paster, magnesium trisilicate, talc, corn starch, keratin, paraffin, colloidal  
30 silica, potato starch, urea and other carriers suitable for use in manufacturing preparations, in solid, semisolid, or liquid form, and in addition auxiliary, stabilizing, thickening and coloring agents and perfumes may be used. The active compound is included in a pharmaceutical composition in an effective amount sufficient to produce the desired effect upon the process or condition of the diseases.

35 The active ingredient can be formulated into, for example, preparations for oral application, preparations for injection, preparations for external application, preparations

for inhalation, preparations for application to mucous membranes.

Mammals which may be treated by the present invention include livestock mammals such as cows, horses, etc., domestic animals such as dogs, cats, rats, etc. and humans, preferably humans.

5 While the dosage of therapeutically effective amount of the compound (I) will vary depending upon the age and condition of each individual patient, an average single dose to a human patient of about 0.01 mg, 0.1 mg, 1 mg, 10 mg, 50 mg, 100 mg, 250 mg, 500 mg, and 1000 mg of the compound (I) may be effective for treating the above-mentioned diseases. In general, amounts between 0.01 mg/body and about 1,000  
10 mg/body may be administered per day.

In order to illustrate the usefulness of the object compound (I), the pharmacological test data of the compound (I) are shown in the following.

#### A. Test Compound

15 5-chloro-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone  
(Compound A: The compound of Example 1)

8-chloro-2-[(1E)-3-[4-(4-fluorophenyl)-3,6-dihydro-1(2H)-pyridinyl]-1-propenyl]-4(3H)-quinazolinone

(Compound B: The compound of Example 33 (1))

20 8-Chloro-2-[[4-(4-pyridinyl)-3,6-dihydro-1(2H)-pyridinyl] propyl]-4(3H)-quinazolinone

(Compound C: The compound of Example 35 (15))

8-methyl-2-[3-(1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)propyl]-4(3H)-quinazolinone

25 (Compound D: The compound of Example 38 (2))

#### B. PARP inhibitory activity (In vitro assay)

##### (1) Assay conditions:

The recombinant human PARP (5.3mg protein/ml) were incubated with a test  
30 compound in a 100μl reaction buffer containing the indicated concentration of 1 mCi/ml <sup>32</sup>P-NAD, 50mM Tris-HCl, 25mM MgCl<sub>2</sub>, 1mM DTT (dithiothreitol), 0.05mM NAD (nicotinamido adenine dinucleotide), 1mg/ml activated DNA, pH8.0. Incubation was for 15 minutes at a room temperature and the reaction was stopped by the addition of 200μl of ice-cold 20% trichloroacetic acid followed by rapid filtration through GF/B filters. The  
35 filters were treated with scintillation fluid and acid-insoluble counts were measured for quantification of unit activity.

PARP inhibitory activity (%) =

$$[1 - (\text{enzyme activity with test compound}) / (\text{enzyme activity with vehicle})] \times 100$$

## 5 (2) Result

PARP inhibitory activity (IC<sub>50</sub>) in test compound.

| Test Compound | IC <sub>50</sub> (μM) |
|---------------|-----------------------|
| Compound A    | < 0.5                 |
| Compound B    | < 0.5                 |
| Compound C    | < 0.5                 |
| Compound D    | < 0.5                 |

## C. Effect of test compound on the level of striatal dopamine and its metabolite in mice

MPTP(N-methyl-1,2,3,6-tetrahydropyridine)-induced Parkinson's model

## 10 (1) Method

Mice received four i.p. injections of MPTP-HCl (20mg/kg) in saline at 2hours intervals and two i.p. injections of Test compound at 30minutes before 1st injection and 3rd injection of MPTP.

Four days after the last MPTP injection, mice were sacrificed, brains were quickly removed, and striata were dissected out on an ice-cold glass Petri dish. Samples were homogenized in a buffer of 0.1M perchloric acid containing isoproterenol as internal standard. HPLC with electrochemical detection was used to measure striatal levels of of DA (dopamine), DOPAC (dihydroxyphenylacetic acid) and HVA (homovanilic acid).

## 20 (2) Results

The level of DA, DOPAC and HVA were expressed as a percentage of Normal taken as the 100%.

|                             | Dopamine levels |
|-----------------------------|-----------------|
| Normal                      | 100             |
| MPTP                        | 21              |
| MPTP + Compound A (32mg/kg) | 59*             |

|                             | DOPAC levels |
|-----------------------------|--------------|
| Normal                      | 100          |
| MPTP                        | 25           |
| MPTP + Compound A (32mg/kg) | 58*          |

25

|                             | HVA levels |
|-----------------------------|------------|
| Normal                      | 100        |
| MPTP                        | 40         |
| MPTP + Compound A (32mg/kg) | 64*        |

\* P<0.05 vs MPTP (by Student's t-test)

This invention relates to novel Quinazoline compounds had a potent PARP inhibitory activity. PARP inhibitors including this invention relates to novel quinazoline compounds were effective in preventing reduction of striatal DA and its metabolite induced by MPTP treatment in mice. Therefore, it suggests that these compounds may have protective benefit in the treatment of neurodegenerative disease such as Parkinson's disease.

Abbreviations used herein have the following meanings:

| ABBREVIATION | DEFINITION  |
|--------------|-------------|
| Me           | methyl      |
| Et           | ethyl       |
| tBu          | tert-buthyl |
| Bzl          | benzyl      |
| Ph           | phenyl      |
| Ac           | acetyl      |
| Bz           | benzoyl     |

Any patents, patent applications, and publications cited herein are incorporated by reference.

#### Best Mode for Carrying out the Invention

The following Preparation and Examples are given for the purpose of illustrating the present invention in detail, but are not to be construed to limit the scope of the present invention.

#### Preparation 1

2-Amino-6-chlorobenzoic acid (150g, 874mmol) was added slowly to thionyl chloride (383mL, 5.25mol) at 5 °C and the mixture was refluxed for 2 hours. Thionyl chloride was removed in vacuo. Toluene was added and removed in vacuo. The obtained acid chloride was dissolved in dioxane (750 mL). The solution was added



dropwise to  $\text{NH}_4\text{OH}$  (27%, 835mL, 4.37mol) at 5 °C. The mixture was concentrated in vacuo. The reaction mixture was extracted with ethyl acetate. Hexane was added to the organic layer, and the precipitate was corrected with filtration. The resulting crystals were dried to give 2-amino-6-chlorobenzamide (95.8g, 577mmol, 64%).

5  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 4.84 (2H, br.s), 5.97(1H, br.s), 6.20(1H, br.s), 6.60(1H, d,  $J=8.2$  Hz), 6.73 (1H, d,  $J=8.0$  Hz), and 7.07 (1H, t,  $J=8.1$  Hz)

Mass (m/z): 171 ( $\text{M}^++1$ )

#### Preparation 2

10 To a mixture of 2-amino-6-chlorobenzamide (100g, 586mmol) and diisopropyl-ethylamine (123mL, 703mmol) in THF (1L) 4-pentenoyl chloride (74.4mL, 674mmol) was added dropwise at 5 °C. The mixture was stirred for 30 minutes. Saturated sodium hydrogen carbonate aqueous solution was added and the precipitate was corrected by filtration and washed with water to give

15 2-chloro-6-(4-pentenoylamino)benzamide, which was used without further purification.

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 2.47(4H, s), 5.03 (1H, dd,  $J=10.1\text{Hz}$ ,  $<1\text{Hz}$ ), 5.13 (1H, dt,  $J=7.9\text{Hz}$ ,  $<1\text{Hz}$ ), 5.85 (1H, m), 6.15(1H, br.s), 6.28(1H, br.s), 7.34 (1H, t,  $J=8.3$  Hz), 7.16 (1H, d,  $J=9.1$  Hz), 8.23 (1H, d,  $J=8.4$  Hz), and 9.26 (1H, br.s).

Mass (m/z): 253 ( $\text{M}^++1$ )

20

#### Preparation 3

2-Chloro-6-(4-pentenoylamino)benzamide (148g, 586mmol) was dissolved in dioxane (1L), and 1N NaOH aqueous solution (1.17L) was added. The reaction mixture was stirred at room temperature for 2.5 hours. The reaction mixture was concentrated in  
25 vacuo, then the resulting solution was neutralized with 1N HCl aqueous solution. The precipitate was corrected with filtration and washed with ether to give 2-(3-butenyl)-5-chloro-4(3H)-quinazolinone (96.6g, 0.41mmol, 70% for two steps) as colorless crystals.

$^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 2.66 (2H, q,  $J=7.3$  Hz), 2.87 (2H, t,  $J=7.6$  Hz), 5.05 (1H, d,  $J=9.9$  Hz), 5.15 (1H, d,  $J=17.3\text{Hz}$ ), 5.09 (1H, m), 7.45 (1H, m), and 7.66 (2H, m).

30

Mass (m/z): 235 ( $\text{M}^++1$ )

#### Preparation 4

$\text{OsO}_4$  (2.5% t-BuOH solution, 23.8mL, 2.34mmol) was added to 10% aqueous  
35 dioxane solution of 2-(3-butenyl)-5-chloro-4(3H)-quinazolinone (55g, 234mmol). After stirring for 10 minutes,  $\text{NaIO}_4$  (110g, 516mmol) was added to the mixture. The mixture

was stirred at room temperature for 4 hours. The reaction mixture was extracted with AcOEt, and washed with 10% Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> and brine. The organic layer was dried over MgSO<sub>4</sub> and the solvent was removed in vacuo. The residual yellow solid was purified by silica gel chromatography eluting with chloroform and methanol (100:1-100:2) to give  
5 8-chloro-1-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazoline-9(1H)-one (26.5g, 110mmol, 48%) was obtained as colorless powder.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 2.22 (1H, m), 2.50 (1H, m), 3.04 (1H, m), 3.35 (1H, m),  
4.36 (1H, br.s), 6.28 (1H, m), 7.46 (1H, m), and 7.59 (2H, m).

Mass (m/z): 237 (M<sup>+</sup>+1)

10

#### Preparation 5.

Benzylchloride (3.25mL, 28.2mmol) was added to the mixture of 4-phenyl-4-hydroxypiperidine and t-BuOK (3.17g, 28.2mmol) in t-butanol (70mL), and the mixture was refluxed for 2 hours. Methanol (30mL) was added to the mixture and  
15 inorganic solid was filtered off. The solution was concentrated in vacuo and extracted with AcOEt, washed with brine. Solvent was removed in vacuo, and the residual solid was washed with diisopropylether/hexane (1:10) to give

1-benzyl-4-hydroxy-4-phenylpiperidine (6.32g, 23.6mmol, 84%) as colorless powder.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.74(2H, dm, J=14.1Hz), 2.18 (2H, td, J=13.0 Hz, 4.4 Hz),  
20 2.48 (2H, tm, J=13.0 Hz), 2.80 (2H, dm, J=11.1 Hz), 3.59 (2H, s), 7.23-7.30 (3H, m), 7.33-7.38 (5H, m), and 7.52 (2H, dm, J=7.9 Hz).

Mass (m/z): 268 (M<sup>+</sup>+1).

#### Preparation 6

25 Sulfuric acid (16.7mL, 314mmol) was added dropwise to dispersion of 1-benzyl-4-hydroxy-4-phenylpiperidine (6g, 22.4mmol) in acetonitrile (25.8mL, 494mmol) at 0 °C, and the mixture was stirred at room temperature for 30 minutes. The reaction mixture was poured into cold water. The solution was adjusted to pH 9 with saturated sodium hydrogen carbonate aqueous solution and 1N NaOH aqueous solution. The mixture  
30 was extracted with AcOEt, washed with saturated sodium hydrogen carbonate aqueous solution and brine. Solvent was removed in vacuo. Residual colorless solid was washed with ether to give 4-acetoamide-1-benzyl-4-phenylpiperidine (5.8g, 19.0mmol, 84%) as colorless powder.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 2.03 (3H, m), 2.12 (2H, m), 2.30 (4H, m), 2.80 (2H, d,  
35 J=12.2 Hz), 3.53 (2H, s), 5.53 (1H, br.s), and 7.4-7.18 (10H, m).

Mass (m/z): 309 (M<sup>+</sup>+1)

Preparation 7

4-Acetoamide-1-benzyl-4-phenylpiperidine (2.7g, 8.75mmol) was dissolved in 6N aqueous HCl (7.27mL, 43.8mmol) at 130 °C. After the solution was cooled to room temperature, 1N NaOH aqueous solution was added. The reaction mixture was extracted with AcOEt, washed with saturated sodium hydrogen carbonate aqueous solution. The organic layer was dried over MgSO<sub>4</sub> and the solvent was removed in vacuo. The residual pale yellow oil was purified by silica gel chromatography eluting with chloroform and methanol (100:5-100:20) to give 4-amino-1-benzyl-4-phenylpiperidine (1.7g, 6.38mmol, 73%) as pale yellow oil.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.70(2H, m), 2.20 (2H, m), 2.50 (2H, m), 2.71 (2H, m), 3.57 (2H, s), 7.25 (2H, m), 7.35 (6H, tm, J=7.6 Hz), and 7.52 (2H, dm, J=7.24 Hz).

Mass (m/z): 267 (M<sup>+</sup>+1)

15 Preparation 8

4-Amino-1-benzyl-4-phenylpiperidine (500mg, 1.88mmol) and HCO<sub>2</sub>NH<sub>4</sub> (1.18g, 18.8mmol), and Pd-C (10%, 500mg) were dispersed in ethanol/H<sub>2</sub>O (10mL/10mL). The mixture was refluxed for 4 hours. Insoluble products were filtrated off, and the solvent was removed in vacuo. The residue was purified by reverse phase chromatography eluting by water to give 4-amino-4-phenylpiperidine (20mg, 11.3mmol, 13.7%) as colorless solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.73 (2H, m), 2.16 (2H, m), 2.79 (2H, m), 3.02 (2H, m), 7.22 (1H, tm, J=7.3 Hz), 7.35 (2H, tm, J=8.0 Hz), and 7.51 (2H, tm, J=7.3 Hz).

Mass (m/z): 177 (M<sup>+</sup>+1)

25

Preparation 9

Oxalyl chloride was added to a solution of 4-(1-phenyl-4-piperidyl)-butanoic acid (200 mg, 0.809 mmol) in DMF (5 mL) under ice water bath, then the mixture was stirred for 1 hour.

30 To a solution of 2-carbamoylaniline (110 mg, 0.809 mmol) in DMF (5 mL) was added N-ethyl-diisopropylamine (0.169 mL, 0.97 mmol) under ice water bath, then the previous solution was added dropwise. After stirring 2 hours at room temperature, the mixture was poured into ice water, extracted with ethyl acetate twice, washed with saturated aqueous NaHCO<sub>3</sub> and brine, and dried over sodium sulfate. Evaporation of the solvent  
35 gave the residue, and purified by silica gel chromatography eluting with chloroform and methanol (20:1) to give 2-[4-(1-phenyl-4-piperidyl)-butanoylamino]benzamide (100 mg,

0.26 mmol, 34%) as a pale yellow powder.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.26-1.50 (5H, m), 1.72-1.89 (4H, m), 2.42 (2H, t, J=7.5 Hz), 2.68 (2H, t, J=7.0 Hz), 3.66 (2H, d, J=7.0 Hz), 6.81 (1H, t, J=7.8 Hz), 6.94 (2H, d, J=7.8 Hz), 7.08 (1H, t, J=7.8 Hz), 7.24 (2H, d, J=7.8 Hz), 7.42-7.56 (2H, m), 8.67 (1H, d, J=7.8 Hz), 11.15 (1H, s)

Mass (m/z): 366 (M<sup>+</sup>)

#### Preparation 10-(1)

Under a nitrogen atmosphere, a solution of butyllithium (1.6 M in hexane, 10.8 mL) was added dropwise to a solution of 1-bromo-4-methoxybenzene (3.04 g, 16.3 mmol) in tetrahydrofuran (30 mL) at -78 °C. The mixture was stirred at the temperature for 30 minutes, and a solution of tert-butyl 4-oxo-1-piperidinecarboxylate (2.7 g, 13.6 mmol) in tetrahydrofuran (20 mL) was added dropwise. The mixture was allowed to warm to -20 °C with stirring for 2 hours. The reaction was quenched by addition of saturated aqueous ammonium chloride, and the organic materials were extracted with ethyl acetate. The organic layer was washed with water and brine and dried over magnesium sulfate.

Purification over silica gel chromatography gave tert-butyl

4-hydroxy-4-(4-methoxyphenyl)-1-piperidinecarboxylate (3.04 g, 73.0 %) as oil.

<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 1.48 (9H, s), 1.73 (2H, br d, J=12.0 Hz), 1.97 (2H, dt, J=12.5, 2.4 Hz), 3.24 (2H, br t, J=11.6 Hz), 3.81 (3H, s), 4.02 (2H, br d, J=9.8 Hz), 6.89 (2H, d, J=8.9 Hz), 7.39 (2H, d, J=8.9 Hz)

Mass (APCI+, 50V): 330.3 (M<sup>+</sup>+Na)

#### Preparation 10-(2)

Trifluoroacetic acid (7.6 mL, 98.9 mmol) was added to an ice-cooled solution of tert-butyl 4-hydroxy-4-(4-methoxyphenyl)-1-piperidinecarboxylate (3.04 g, 9.89 mmol) in dichloromethane (15 mL), and the mixture was stirred at 0 °C for 1 hour. Trifluoroacetic acid and dichloromethane were removed in vacuo, and the crude product was treated with ethyl acetate and aqueous sodium hydrogen carbonate. The organic layer was separated, and dried over sodium sulfate. The evaporated residue was treated with a solution of hydrogen chloride (4 M in ethyl acetate, 5 mL) in ice-cooled ethyl acetate (15 mL) for 1 hour to give 4-(4-methoxyphenyl)-1,2,3,6-tetrahydropyridine hydrochloride (1.63 g, 73.0 %) as powder.

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.66 (2H, br), 3.27 (2H, br), 3.70 (2H, br), 3.76 (3H, s), 6.08 (1H, m), 6.94 (2H, d, J=8.8 Hz), 7.42 (2H, d, J=8.8 Hz), 9.29 (2H, br)

Mass (API-ES+): 190.4 (M<sup>+</sup>+H)

Preparation 11

Tert-butyl 4-hydroxy-4-[4-(trifluoromethyl)phenyl]-1-piperidinecarboxylate was prepared in a similar procedure to that of Preparation 10-(1), which was used for the next step (Preparation 12).

5

Preparation 12

Methanesulfonyl chloride (3.44 mL, 44.4 mmol) was added dropwise to a solution of tert-butyl 4-hydroxy-4-[4-(trifluoromethyl)phenyl]-1-piperidinecarboxylate (includes tert-butyl 4-oxo-1-piperidinecarboxylate, 5.11 g) in triethylamine (20.6 mL) and dichloromethane (60 mL) at  $-78^{\circ}\text{C}$ . 4-Dimethylaminopyridine (90 mg, 0.74 mmol) was added, and the mixture was allowed to warm to  $0^{\circ}\text{C}$  and was stirred for 2 hours at  $0^{\circ}\text{C}$ .

Quenched with water, and the organic materials were extracted with chloroform. Solvents were removed in vacuo, and the residue was dissolved in dichloromethane (50 mL) and triethylamine (20 mL), and stirred for 2 days at room temperature. Quenched by the addition of water, and the product was extracted with  $\text{CHCl}_3$ . Purification over silica gel (hexane:ethyl acetate=10:1) gave tert-butyl 3,6-tetrahydro-4-[4-(trifluoromethyl)phenyl]-1(2H)-pyridinecarboxylate (3.57 g, 73.7 %).  $^1\text{H}$  NMR (200MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 1.50 (9H, s), 2.53 (2H, m), 3.65 (2H, t,  $J=5.7$  Hz), 4.10 (2H, q,  $J=2.8$  Hz), 6.12 (1H, br), 7.46 (2H, d,  $J=8.4$  Hz), 7.58 (2H, d,  $J=8.5$  Hz) Mass (API-ES): 350.3 ( $\text{M}^+ + \text{Na}$ )

Preparation 13

A solution of hydrogen chloride (4 M in ethyl acetate, 16.4 mL) was added to a solution of tert-butyl 3,6-tetrahydro-4-[4-(trifluoromethyl)phenyl]-1(2H)-pyridinecarboxylate (3.57 g, 10.9 mmol) in ethyl acetate (4 mL) at  $0^{\circ}\text{C}$ . The mixture was stirred for 1.5 hr at the temperature. Evaporated to dryness, and the residue was washed with ethyl acetate and diisopropyl ether to give 4-[4-(trifluoromethyl)phenyl]-1,2,3,6-tetrahydropyridine hydrochloride (2.61 g, 90.8 %) as white powder.  $^1\text{H}$  NMR (200MHz,  $\text{DMSO}-d_6$ ,  $\delta$ ): 2.73 (2H, br), 3.32 (2H, t,  $J=6.0$  Hz), 3.78 (2H, m), 6.37 (1H, br), 7.70 (2H, d,  $J=8.9$  Hz), 7.76 (2H, d,  $J=9.0$  Hz), 9.38 (2H, br s) Mass (API-ES): 228.3 ( $\text{M}^+ + \text{H}$ )

Preparation 14

Under a nitrogen atmosphere, a mixture of tert-butyl 4-(((trifluoromethyl)sulfonyl)oxy)-3,6-dihydro-1(2H)-pyridinecarboxylate (1.0 g, 3.02

mmol), 4-cyanophenylboronic acid (532 mg, 3.62 mmol), triethylamine (1.26 mL, 9.05 mmol) and tetrakis(triphenylphosphine)palladium (35 mg, 0.030 mmol) in N,N-dimethylformamide (15 mL) was stirred for 2 hours at 100 °C. Quenched with water, and the product was extracted with ethyl acetate. Solvents were removed in vacuo  
5 (treated with toluene once azeotropically) to give the crude product. It was treated with a solution of hydrogen chloride (4 M in ethyl acetate, 5 mL) in ice-cooled ethyl acetate (7 mL) for 1 hour. The precipitate was collected by filtration and washed with ethyl acetate and diisopropyl ether to give 4-(1,2,3,6-tetrahydro-4-pyridinyl)benzonitrile hydrochloride (460 mg, 54.5 %) as white powder.  
10 <sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.50 (2H, m), 2.70 (2H, br), 3.80 (2H, br), 6.42 (1H, m), 7.68 (2H, d, J=8.6 Hz), 7.86 (2H, d, J=8.6 Hz), 9.05 (2H, br)

#### Preparation 15

A mixture of 2-amino-3-iodobenzoic acid (1.12 g) and thionyl chloride (3.11 ml)  
15 was refluxed for 1 hour. The mixture was cooled, concentrated and co-evaporated with toluene twice. To 28% ammonia aqueous solution was added dropwise a solution of the residue in dichloromethane, then the resulting powder was collected, washed with water and dried in vacuo to give the 2-amino-3-iodobenzamide.  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 6.37 (1H, t, J=7.8 Hz), 6.58 (2H, brs), 7.30 (1H, brs), 7.59 (1H, dd,  
20 J=1.4 Hz, J=7.8 Hz), 7.90 (1H, brs).  
Mass (ESI): 285.1 (M<sup>+</sup>+Na)

#### Preparation 16

The following compounds are prepared in a similar manner to that of Preparation  
25 15.

(1) 2-Amino-3-ethylbenzamide

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 1.13 (3H, t, J=7.4 Hz), 2.45 (2H, q, J=7.4 Hz), 6.20-6.70 (3H, m), 6.80-7.20 (2H, m), 7.42 (1H, dd, J=1.3, 7.9 Hz), 7.71 (1H, brs)

Mass (ESI): 187.2 (M<sup>+</sup>+Na)

30 (2) 2-amino-3-bromobenzamide

Mass (ESI): 239.1 (M<sup>+</sup>+Na)

#### Preparation 17

Under a nitrogen atmosphere, a solution of 4-bromobutyryl chloride (4.9 g, 26.4  
35 mmol) in dichloromethane (10 mL) was added dropwise to the solution of 2-aminobenzamide (3.0 g, 22 mmol) in pyridine (18 mL, 220 mmol) and dichloromethane

(15 mL) at 0 °C. The mixture was stirred for 1.5 hours at 0 °C. The reaction mixture was poured into ice-cooled 1N hydrochloric acid, and the product was extracted with chloroform. The organic layer was washed with 1N hydrochloric acid and water and dried over sodium sulfate. The crude product was triturated with toluene to give

5 2-[(4-bromobutanoyl)amino]benzamide (5.11 g, 81.3 %) as powder.

<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 2.29 (2H, quint., J=6.8 Hz), 2.61 (2H, t, J=7.2 Hz), 3.52 (2H, t, J=6.4 Hz), 5.5-6.5 (2H, br), 7.09 (1H, dt, J=7.6, 1.1 Hz), 7.51 (1H, t, J=7.6 Hz), 7.53 (1H, d, J=7.6 Hz), 8.62 (1H, d, J=8.5 Hz), 11.25 (1H, s)

Mass (API-ES) 307.1, 309.1 (M<sup>+</sup>+Na)

10

#### Preparation 18

The following compounds are prepared in a similar manner to that of Preparation 17.

- (1) 2-[(4-Bromobutanoyl)amino]-3-iodobenzamide  
15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 1.90-2.30 (2H, m), 2.43 (2H, t, J=7.4 Hz), 3.61 (2H, t, J=6.7 Hz), 7.10 (1H, t, J=7.8 Hz), 7.96 (1H, dd, J=1.3 Hz, J=7.8 Hz), 9.66 (1H, brs)  
Mass (ESI): 433.0 (M<sup>+</sup>+Na)
- (2) 3-Bromo-2-[(4-bromobutanoyl)amino]benzamide  
20 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 1.80 - 2.10 (2H, m), 2.69 (2H, t, J=7.3 Hz), 3.51 (2H, t, J=6.3 Hz), 7.10-9.70 (6H, m)  
Mass (ESI): 387.0 (M<sup>+</sup>+Na)
- (3) 2-[(4-Bromobutanoyl)amino]-3-ethylbenzamide  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 0.90-3.80 (11H, m), 7.00-9.70 (6H, m)  
25 Mass (ESI): 335.1 (M<sup>+</sup>+H)
- (4) 2-[(4-bromobutanoyl)amino]-6-fluorobenzamide  
MS (API-ES): 325.0 (M<sup>+</sup>+Na)
- (5) 2-[(3-bromopropanoyl)amino]benzamide  
MS (API-ES): 293.1 (M<sup>+</sup>+Na)

30

#### Preparation 19

A mixture of 2-aminobenzamide (45 mg),  
4-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)pentanoic acid (85.7 mg),  
O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (628 mg)  
35 and diisopropylethylamine (0.288 ml) was stirred at room temperature overnight. The mixture was diluted with water and extracted with dichloromethane three times. The

combined extracts were washed with water three times, dried over magnesium sulfate and concentrated. The residue was purified by preparative thin layer chromatography using 10% methanol in dichloromethane as an eluent to give the

2-[[4-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)pentanoyl]amino]benzamide.

5 Mass (ESI): 388.3 ( $M^+ + H$ )

#### Preparation 20

Under a nitrogen atmosphere, triethylamine (0.73 mL, 5.26 mmol) was added to a solution of 2-[(4-bromobutanoyl)amino]benzamide (500 mg, 1.75 mmol) and  
 10 4-phenyl-1,2,3,6-tetrahydropyridine hydrochloride (412 mg, 2.10 mmol) in N,N-dimethylformamide (5 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 24 hour. The reaction was quenched with water, and the product was extracted with chloroform. The organic layer was washed with water and dried over sodium sulfate. Purification over silica gel chromatography gave  
 15 2-[[4-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)butanoyl]amino]benzamide (477 mg, 74.8 %) as pale-yellow powder.

$^1H$  NMR (200MHz,  $CDCl_3$ ,  $\delta$ ): 2.01 (2H, quint.,  $J=7.3$  Hz), 2.41-2.56 (4H, m), 2.72 (2H, t,  $J=5.4$  Hz), 3.76 (2H, d,  $J=5.7$  Hz), 5.4-6.3 (2H, br), 6.05 (1H, m), 7.05 (1H, t,  $J=7.0$  Hz), 7.21-7.37 (6H, m), 7.45-7.51 (2H, m), 8.64 (1H, d,  $J=8.6$  Hz)

20 Mass (APCI): 364.20 ( $M^+ + H$ )

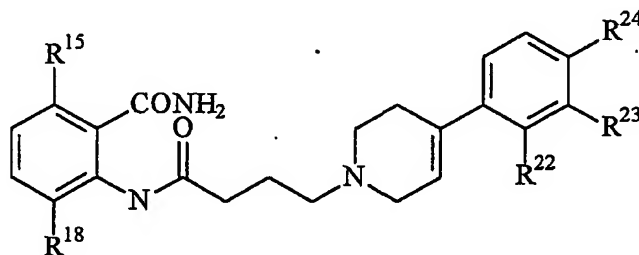
#### Preparation 21

The following compounds are prepared in a similar manner to that of Preparation

20.

25

30



| No. | R <sup>15</sup> | R <sup>18</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup> |  |
|-----|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (1) | H               | H               | H               | H               | H               | $^1H$ NMR (DMSO- $d_6$ , $\delta$ ): 1.82 (2H, m), 2.33 (2H, t, $J=7.3$ Hz), 2.35-2.70 (4H, m), 2.65 (2H, t, $J=5.4$ Hz), 3.1 (2H, d, $J=2.8$ Hz), 6.15 (1H, s), 6.80-7.80 (9H, m), 7.96 (H, dd, $J=1.4$ Hz, $J=7.9$ Hz), 9.62 (1H, s)<br>Mass (ESI): 490.2 ( $M^+ + Na$ ) |



| No.  | R <sup>15</sup> | R <sup>18</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup>    |   |
|------|-----------------|-----------------|-----------------|-----------------|--------------------|---|
| (2)  | H               | Br              | H               | H               | H                  | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.70-2.00 (2H, m), 2.10-2.90 (8H, m), 3.22 (2H, d, J=6.1 Hz), 6.16 (1H, s), 7.10-8.00 (10H, m), 9.62 (1H, brs)<br>Mass (APCI): 442.13 (M <sup>+</sup> +H)   |
| (3)  | H               | Et              | H               | H               | H                  | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.10 (3H, t, J=7.5 Hz), 1.60-1.90 (2H, m), 2.20-2.80 (10H, m), 3.09 (2H, d, J=2.6 Hz), 6.16 (1H, s), 7.10-7.70 (10H, m), 9.38 (1H, s)<br>Mass (APCI): 392.07 (M <sup>+</sup> +H)  |
| (4)  | H               | H               | F               | H               | H                  | Mass (APCI): 381.93 (M <sup>+</sup> +H)   |
| (5)  | H               | H               | H               | F               | H                  | Mass (APCI): 381.93 (M <sup>+</sup> +H)   |
| (6)  | H               | H               | OMe             | H               | H                  | Mass (APCI): 394.20 (M <sup>+</sup> +H)   |
| (7)  | H               | H               | H               | OMe             | H                  | Mass (APCI): 394.13 (M <sup>+</sup> +H)   |
| (8)  | H               | H               | H               | H               | OEt                | Mass (API-ES): 408.3 (M <sup>+</sup> +H)  |
| (9)  | H               | H               | H               | H               | SMe                | Mass (API-ES): 410.2 (M <sup>+</sup> +H)  |
| (10) | H               | H               | H               | H               | OCF <sub>3</sub>   | Mass (API-ES): 448.2 (M <sup>+</sup> +H)  |
| (11) | H               | H               | H               | H               | Et                 | Mass (APCI) 390.07 (M <sup>+</sup> -H)  |
| (12) | H               | H               | H               | H               | N(Me) <sub>2</sub> | Mass (APCI): 406.93 (M <sup>+</sup> +H)   |
| (13) | H               | H               | H               | H               | t-Bt               | Mass (APCI): 420.13 (M <sup>+</sup> +H)   |
| (14) | H               | H               | H               | H               | Ph                 | Mass (APCI): 440.13 (M <sup>+</sup> +H)   |
| (15) | H               | H               | H               | H               | OPh                | Mass (APCI): 456.13 (M <sup>+</sup> +H)   |
| (16) | H               | H               | H               | H               | Ac                 | Mass (APCI): 406.07 (M <sup>+</sup> +H)   |
| (17) | F               | H               | H               | H               | H                  | Mass (API-ES): 382.4 (M <sup>+</sup> +H)  |
| (18) | F               | H               | H               | H               | OMe                | Mass (APCI): 411.80 (M <sup>+</sup> +H)   |
| (19) | F               | H               | H               | H               | F                  | Mass (APCI): 399.87 (M <sup>+</sup> +H)   |
| (20) | H               | Cl              | H               | H               | CN                 | Mass (API-ES): 423.3 (M <sup>+</sup> +H)  |
| (21) | H               | Cl              | H               | H               | Ac                 | Mass (APCI): 440.07 (M <sup>+</sup> +H)   |
| (22) | Cl              | H               | H               | H               | CN                 | Mass (API-ES): 423.3 (M <sup>+</sup> +H)  |
| (23) | H               | H               | H               | H               | Me                 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.01 (2H, quint., J=7.3 Hz), 2.45-2.59 (4H, m), 2.71 (2H, t, J=5.6 Hz), 3.17 (2H, d, J=3.2 Hz), 5.4-6.4 (2H, br), 6.01 (1H, m), 7.02 (1H, t, J=6.5 Hz), 7.11 (2H, d, J=8.1 Hz), 7.25 (2H, d, J=8.1 Hz), 7.45-7.53 (2H, m), 8.65 (1H, d, J=8.6 Hz), 11.14 (1H, s)<br>Mass (APCI): 378.20 (M <sup>+</sup> +H)       |
| (24) | H               | H               | H               | H               | F                  | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.00 (2H, quint., J=7.3 Hz), 2.45-2.59 (6H, m), 2.71 (2H, t, J=5.6 Hz), 3.16 (2H, q, J=2.2 Hz), 5.4-6.3 (2H, br), 5.99 (1H, m), 6.97 (2H, t, J=8.8 Hz), 7.05 (1H, t, J=7.6 Hz), 7.31 (2H, dd, J=8.8, 5.4 Hz), 7.45-7.52 (2H, m), 8.65 (1H, d, J=8.6 Hz), 11.16 (1H, s)<br>Mass (APCI): 381.93 (M <sup>+</sup> +H) |

| No.  | R <sup>15</sup> | R <sup>18</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup>    |   |
|------|-----------------|-----------------|-----------------|-----------------|--------------------|---|
| (25) | H               | H               | H               | H               | OMe                | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.00 (2H, quint., J=7.3 Hz), 2.45-2.58 (6H, m), 2.70 (2H, t, J=5.6 Hz), 3.16 (2H, q, J=2.8 Hz), 3.80 (3H, s), 5.6-6.4 (2H, br), 5.96 (1H, m), 8.37 (2H, d, J=8.8 Hz), 7.04 (1H, t, J=8.7 Hz), 7.29 (2H, d, J=8.8 Hz), 7.44-7.52 (2H, m), 8.63 (1H, dd, J=8.6, 1.2 Hz), 11.15 (1H, s)<br>Mass (APCI): 394.13 (M <sup>+</sup> +H)                                 |
| (26) | H               | H               | H               | H               | CF <sub>3</sub>    | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.01 (2H, quint., J=7.2 Hz), 2.46-2.60 (6H, m), 2.73 (2H, t, J=5.6 Hz), 3.20 (2H, q, J=2.9 Hz), 5.5-6.4 (2H, br), 6.14 (1H, m), 7.05 (1H, t, J=7.4 Hz), 7.41-7.60 (6H, m), 8.65 (1H, dd, J=8.6, 1.2 Hz), 11.17 (1H, s)<br>Mass (APCI): 432.00 (M <sup>+</sup> +H)   |
| (27) | H               | H               | H               | H               | CN                 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.01 (2H, quint., J=7.2 Hz), 2.45-2.61 (6H, m), 2.73 (2H, t, J=5.6 Hz), 3.63 (2H, q, J=6.1 Hz), 5.4-6.3 (2H, br), 6.28 (1H, m), 7.05 (1H, t, J=7.7 Hz), 7.40-7.61 (4H, m), 7.58 (2H, d, J=8.5 Hz), 8.65 (1H, d, J=8.6 Hz), 11.17 (1H, s)<br>Mass (APCI): 389.00 (M <sup>+</sup> +H)   |
| (28) | H               | H               | H               | H               | CH <sub>2</sub> OH | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.75-1.95 (2H, m), 2.3-2.7 (8H, m), 3.07 (2H, d, J=2.7 Hz), 4.47 (2H, d, J=5.6 Hz), 5.12 (1H, t, J=5.6 Hz), 6.11 (1H, s), 7.08 (1H, dt, J=7.4, 1.1 Hz), 7.25 (2H, d, J=8.3 Hz), 7.36 (2H, d, J=8.3 Hz), 7.46 (1H, dt, J=7.4, 1.4 Hz), 7.69 (1H, br s), 7.77 (1H, dd, J=7.9, 1.4 Hz), 8.24 (1H, br s), 8.47 (1H, br s), 11.67 (1H, s)<br>Mass: 394.1 (M <sup>+</sup> ) |
| (29) | H               | Cl              | H               | H               | OMe                | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.7-1.95 (2H, m), 2.3-2.75 (6H, m), 3.09 (2H, s), 3.74 (3H, s), 6.03 (1H, s), 6.88 (2H, d, J=8.9 Hz), 7.25-7.65 (9H, m), 9.65 (1H, s)<br>Mass: 428.1 (M <sup>+</sup> +H)  |
| (30) | H               | Cl              | H               | H               | H                  | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.7-1.95 (2H, m), 2.25-2.7 (6H, m), 3.08 (2H, d, J=2.5 Hz), 6.15 (1H, s), 7.2-7.7 (10H, m)<br>Mass: 398.3 (M <sup>+</sup> +H)   |
| (31) | H               | Cl              | H               | H               | CF <sub>3</sub>    | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.7-1.9 (2H, m), 2.25-2.75 (6H, m), 3.12 (2H, m), 6.33 (1H, s), 7.25-7.70 (9H, m), 9.61 (1H, s)<br>Mass: 466.0 (M <sup>+</sup> )  |
| (32) | H               | Cl              | H               | H               | CH <sub>2</sub> OH | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.7-1.9 (2H, m), 2.25-2.75 (6H, m), 3.08 (2H, m), 4.47 (2H, d, J=5.8 Hz), 5.12 (1H, t, J=5.8 Hz), 6.13 (1H, s), 7.2-7.6 (9H, m), 9.61 (1H, s)<br>Mass: 428.1 (M <sup>+</sup> +H)  |

Preparation 22

The following compounds are prepared in a similar manner to that of Preparation 20.

- (1) 2-({4-[4-(4-methylphenyl)-1-piperidyl]butanoyl}amino)benzamide  
 5 Mass (APCI): 379.93 ( $M^+ + H$ )
- (2) 2-{{4-[4-(4-phenyl-1-piperazinyl)butanoyl]amino}benzamide  
 Mass (APCI): 367.07 ( $M^+ + H$ )

Preparation 23-(1)

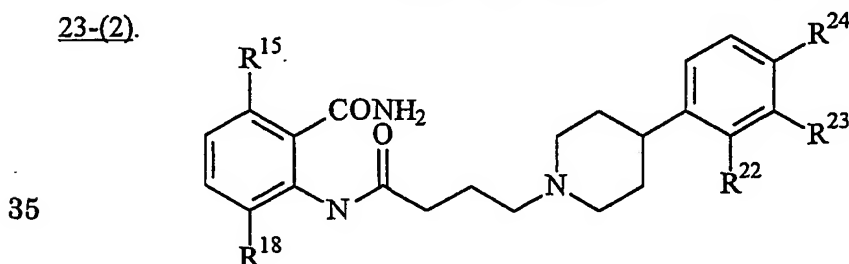
- 10 Palladium hydroxide on carbon (10%, 51.4mg, 0.0366mmol) was added to a solution of
- 2-({4-[4-[4-(methylthio)phenyl]-3,6-dihydro-1(2H)-pyridinyl]butanoyl}amino)benzamide (150 mg, 0.366 mmol) in a mixed solvent of methanol (2 mL) and ethyl acetate (2 mL). Purged by hydrogen (1atm), the mixture was stirred at room temperature for 2 days.
- 15 Purification over silica gel chromatography gave
- 2-[(4-{4-[4-(methylthio)phenyl]-1-piperidyl}butanoyl)amino]benzamide (44 mg, 29.2%) as product.
- Mass (APCI): 412.27 ( $M^+ + H$ )

20 Preparation 23-(2)

- Palladium on carbon (10%, 37.5 mg, 0.0352 mmol) was added to a solution of
- 2-{{4-[4-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)butanoyl]amino}benzamide (128 mg, 0.352 mmol) in a mixed solvent of methanol (2 mL) and ethyl acetate (3 mL). Purged by hydrogen (1 atm), the mixture was stirred at room temperature for 10hour. Purification
- 25 over silica gel chromatography gave
- 2-{{4-[4-(4-phenyl-1-piperidyl)butanoyl]amino}benzamide (91 mg, 70.7 %) as product.
- Mass (APCI): 366.13 ( $M^+ + H$ )

Preparation 24

- 30 The following compounds are prepared in a similar manner to that of Preparation 23-(2).



|      | R <sup>15</sup> | R <sup>18</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup>    |  |
|------|-----------------|-----------------|-----------------|-----------------|--------------------|--|
| (1)  | H               | H               | H               | H               | OEt                | Mass (API-ES): 410.4 (M <sup>+</sup> +H)   |
| (2)  | H               | H               | H               | H               | OCF <sub>3</sub>   | Mass (API-ES): 450.3 (M <sup>+</sup> +H)   |
| (3)  | H               | H               | H               | H               | Et                 | Mass (APCI): 393.87 (M <sup>+</sup> +H)  |
| (4)  | H               | H               | H               | H               | N(Me) <sub>2</sub> | Mass (APCI): 409.27 (M <sup>+</sup> +H)  |
| (5)  | H               | H               | H               | H               | Ph                 | Mass (APCI): 442.27 (M <sup>+</sup> +H)  |
| (6)  | H               | H               | H               | H               | OPh                | Mass (APCI): 458.27 (M <sup>+</sup> +H)  |
| (7)  | H               | H               | H               | H               | Ac                 | Mass (APCI): 408.13 (M <sup>+</sup> +H)  |
| (8)  | H               | H               | H               | H               | OMe                | Mass (APCI): 414.00 (M <sup>+</sup> +H)  |
| (9)  | H               | H               | H               | H               | F                  | Mass (APCI): 401.93 (M <sup>+</sup> +H)  |
| (10) | H               | H               | H               | H               | CF <sub>3</sub>    | Mass (APCI): 434.07 (M <sup>+</sup> +H)  |
| (11) | H               | H               | H               | H               | F                  | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.4-2.1 (8H, m), 2.25-2.6 (5H, m), 2.91 (2H, t, J=11.6 Hz), 6.95-7.20 (5H, m), 7.4-7.5 (1H, m), 7.69 (1H, br s), 7.80 (1H, d, J=7.3 Hz), 8.24 (1H, br s), 8.53 (1H, d, J=8.4 Hz), 11.75 (1H, s)  |
| (12) | H               | H               | H               | H               | OMe                | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.4-2.05 (8H, m), 2.25-2.45 (3H, m), 2.85-3.0 (2H, m), 3.70 (3H, s), 6.79 (2H, d, J=8.7 Hz), 7.02 (2H, d, J=8.7 Hz), 7.11 (1H, dt, J=7.9, 1.1 Hz), 7.48 (1H, dt, J=7.5, 1.1 Hz), 7.69 (1H, br s), 7.81 (1H, dd, J=7.9, 1.4 Hz), 8.24 (1H, br s), 8.53 (1H, dd, J=8.3, 0.9 Hz), 11.75 (1H, s) |

**Preparation 25**

The following compounds are prepared in a similar manner to that of Preparation 20.

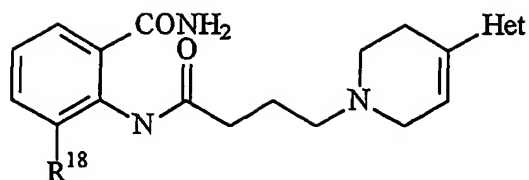
- 5 (1) 2-{{[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propanoyl]amino}benzamide  
MS (APCI): 350.00 (M<sup>+</sup>+H)
- (2) 2-{{[5-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)pentanoyl]amino}benzamide  
<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 1.6-1.9 (4H, m), 2.4-2.6 (6H, m), 2.71 (2H, t, J=5.4 Hz), 3.16 (2H, q, J=2.9 Hz), 5.4-6.5 (2H, br), 6.05 (1H, m), 7.07 (1H, t, J=7.5 Hz),  
10 7.2-7.5 (5H, m), 7.5-7.6 (2H, m), 8.67 (1H, d, J=8.6 Hz), 11.17 (1H, br s)
- (3) 2-{{[3-(4-benzyl-1-piperidyl)propanoyl]amino}benzamide  
MS (APCI): 366.07 (M<sup>+</sup>+H)
- (4) 2-{{[3-(4-benzyl-1-piperazinyl)propanoyl]amino}benzamide  
MS (APCI): 367.00 (M<sup>+</sup>+H)

15

**Preparation 26**

The following compounds are prepared in a similar manner to that of Preparation 20.

5

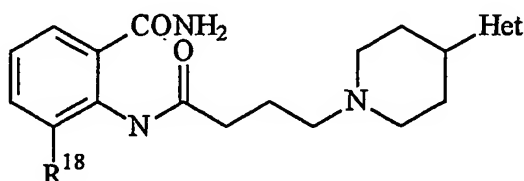


| No.  | R <sup>18</sup> | Het                       |   |
|------|-----------------|---------------------------|---|
| (1)  | H               | 1,3-thiazol-2-yl          | Mass (APCI): 370.73 (M <sup>+</sup> +H)   |
| (2)  | H               | 1-methyl-1H-imidazol-2-yl | Mass (APCI): 367.93 (M <sup>+</sup> +H)   |
| (3)  | H               | 1-methyl-1H-pyrazol-5-yl  | Mass (APCI): 368.00 (M <sup>+</sup> +H)   |
| (4)  | H               | 2-thienyl                 | Mass (APCI): 369.80 (M <sup>+</sup> +H)   |
| (5)  | Cl              | 2-thienyl                 | Mass (APCI): 403.87 (M <sup>+</sup> +H)   |
| (6)  | H               | 3-thienyl                 | Mass (APCI): 369.93 (M <sup>+</sup> +H)   |
| (7)  | Cl              | 3-thienyl                 | Mass (APCI): 403.93 (M <sup>+</sup> +H)   |
| (8)  | H               | 4-methyl-2-thienyl        | Mass (APCI): 384.00 (M <sup>+</sup> +H)   |
| (9)  | H               | 5-acetyl-2-thienyl        | Mass (APCI): 312.07 (M <sup>+</sup> +H)   |
| (10) | H               | 5-chloro-2-thienyl        | Mass (APCI): 403.93 (M <sup>+</sup> +H)   |
| (11) | H               | 5-cyano-2-thienyl         | Mass (APCI): 395.13 (M <sup>+</sup> +H)   |
| (12) | H               | 5-methyl-2-thienyl        | Mass (APCI): 384.3 (M <sup>+</sup> +H)  |
| (13) | H               | 2-pyridinyl               | Mass (APCI): 364.93 (M <sup>+</sup> +H)   |
| (14) | H               | 3-pyridinyl               | Mass (APCI): 365.00 (M <sup>+</sup> +H)   |
|      |                 |                           | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-1.9 (2H, m), 2.25-2.55 (6H, m), 2.6-2.7 (2H, m), 3.12 (2H, d, J=2.5 Hz), 6.49 (1H, s), 7.25-7.6 (5H, m), 8.50 (2H, dd, J=4.6, 1.6 Hz), 9.61 (1H, s) |
| (15) | Cl              | 4-pyridinyl               | Mass: 399.1 (M <sup>+</sup> +H)   |
| (16) | H               | 4-pyridinyl               | Mass (APCI): 364.93 (M <sup>+</sup> +H)   |

#### Preparation 27

The following compounds are prepared in a similar manner to that of Preparation 10 23-(2).

15



| No. | R <sup>18</sup> | Het.                     |  |
|-----|-----------------|--------------------------|--|
| (1) | H               | 1-methyl-1H-pyrazol-5-yl | Mass (API-ES): 370.4 (M <sup>+</sup> +H) |
| (2) | H               | 2-thienyl                | Mass (API-ES): 372.3 (M <sup>+</sup> +H) |
| (3) | H               | 3-thienyl                | MS (APCI): 372.07 (M <sup>+</sup> +H)    |
| (4) | H               | 4-methyl-2-thienyl       | Mass (APCI): 386.13 (M <sup>+</sup> +H)  |
| (5) | H               | 5-methyl-2-thienyl       | Mass (APCI): 386.07 (M <sup>+</sup> +H)  |
| (6) | H               | 4-pyridinyl              | Mass (APCI) 365.00 (M <sup>+</sup> -H)   |

Preparation 28

The following compounds are prepared in a similar manner to that of Preparation

20.

- 5 (1) 2-({4-[4-(4-Chlorophenyl)-3-oxo-1-piperazinyl]butanoyl}amino)benzamide  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 1.70 - 2.00 (2H, m), 2.20 - 2.70 (6H, m), 2.76 (2H, t, J=5.3 Hz), 3.60 (2H, t, J=5.3 Hz), 6.30 - 8.70 (10H, m), 11.71 (1H, brs)  
Mass (ESI): 437.3 (M<sup>+</sup>+Na)
- (2) 2-{{4-(3-phenyl-1-pyrrolidinyl)butanoyl}amino}benzamide  
10 Mass (APCI): 352.27 (M<sup>+</sup>+H)
- (3) 2-{{4-(4-phenyl-1H-imidazol-1-yl)butanoyl}amino}benzamide  
<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 2.25 (2H, quint., J=6.8 Hz), 2.44 (2H, t, J=6.1 Hz), 4.08 (2H, t, J=6.8 Hz), 6.0-6.9 (2H, br), 7.05 (1H, t, J=7.6 Hz), 7.1-7.7 (7H, m), 7.75 (2H, d, J=8.1 Hz), 8.62 (1H, d, J=8.4 Hz), 11.40 (1H, br s)
- 15 (4) 2-{{4-(1,4,5,6-tetrahydrobenzo[f]isoquinolin-3(2H)-yl)butanoyl}amino}benzamide  
Mass (APCI): 389.73 (M<sup>+</sup>+H)
- (5) 2-{{4-(spiro[1H-indene-1,4'-piperidin-1'-yl])butanoyl}amino}benzamide Mass  
(APCI): 390.13 (M<sup>+</sup>+H)
- (6) 2-{{4-(2,3-dihydrospiro[1H-indene-1,4'-piperidin-1'-yl])butanoyl}amino}-  
20 benzamide  
Mass (APCI): 392.20 (M<sup>+</sup>+H)

Preparation 29

- 2-{{4-(4-phenyl-2,3,6,7-tetrahydro-1H-azepin-1-yl)butanoyl}amino}benzamide  
25 (142mg, 25.1%) and 2-{{4-(5-phenyl-2,3,4,7-tetrahydro-1H-azepin-1-yl)butanoyl}-  
amino}benzamide (121mg, 21.4%) were synthesized from 2-[(4-bromobutanoyl)-  
amino]benzamide (427mg, 1.50mmol) and a mixture of 5-phenyl-2,3,4,7-tetrahydro-  
1H-azepine hydrochloride and 4-phenyl-2,3,6,7-tetrahydro-1H-azepine hydrochloride  
(345mg, 1.65mmol) by a similar procedure to the Preparation 20.

2-{{[4-(4-phenyl-2,3,6,7-tetrahydro-1H-azepin-1-yl)butanoyl]amino}benzamide

Mass (APCI): 378.20 ( $M^+ + H$ )

2-{{[4-(5-phenyl-2,3,4,7-tetrahydro-1H-azepin-1-yl)butanoyl]amino}benzamide

Mass (APCI): 378.20 ( $M^+ + H$ )

5

### Preparation 30

The following compounds are prepared in a similar manner to that of Preparation 23-(2).

- (1) 2-{{[4-(4-Phenylhexahydro-1H-azepin-1-yl)butanoyl]amino}benzamide  
 10 Mass (APCI): 380.27 ( $M^+ + H$ )
- (2) 2-{{[4-(cis-1,4,4a,5,6,10b-hexahydrobenz[f]isoquinolin-3(2H)-yl)butanoyl]-  
 amino}benzamide  
 Mass (API-ES): 392.4 ( $M^+ + H$ )

### 15 Preparation 31

Dimethylformamide (1.25 mL, 16.2 mmol) and oxaryl chloride (1.41 mL, 16.2 mmol) were added to a solution of 6-[(benzyloxy)carbonylamino]hexanoic acid (3.9 g, 14.7 mmol) in dichloromethane (5 mL) at 5 °C. The prepared 6-{{[(benzyloxy)carbonyl]amino}hexanoyl chloride was added to a solution of  
 20 2-aminobenzamide and diisopropylethylamine (2.8mL, 1.1eq) in dichloromethane (5mL) at 5 °C. The mixture was stirred at room temperature for 2 hours. The mixture was extracted with AcOEt, and washed with saturated sodium hydrogen carbonate aqueous solution and brine. The organic layer was dried over  $MgSO_4$  and the solvent was removed in vacuo to give 2-{{[5-[(benzyloxy)carbonylamino]hexanoyl]amino}benzamide (2.8 g, 7.3  
 25 mmol, 50 %) as yellow oil.  
 Mass: 384 ( $M^+ + 1$ )

### Example 1

1,2,3,6-Tetrahydro-4-phenylpyridine (54.8g, 280mmol) was added to the 10%  
 30 aqueous acetonitrile solution of  
 8-chloro-1-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazoline-9(1H)-one (26.5g, 112mmol),  
 then sodium cyanoborohydride (10.5g, 168mmol) and acetic acid (8.9mL, 157mmol) was  
 added to the reaction mixture. The mixture was stirred at room temperature over night.  
 Saturated sodium hydrogen carbonate aqueous solution was added to the reaction mixture.  
 35 The precipitate was corrected with filtration and purified by silica gel chromatography  
 eluting with chloroform and methanol (100:1-100:2). The resulting solid was

recrystallized from 10% aqueous acetonitrile to give

5-chloro-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone (17g, 44mmol, 40%) as colorless fine needle.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 2.05 (2H, quint, J=6.2 Hz), 2.66 (2H, t, J=6.2 Hz),  
5        2.80-2.92 (6H, m), 3.31 (2H, m), 6.118 (1H, s), 7.32-7.47 (6H, m), and 7.55 (2H, m).

Mass (m/z): 380 (M<sup>+</sup>+1)

### Example 2

10        4-Phenylpiperidine hydrochloride (334mg, 1.69mmol) was added to the 10% aqueous acetonitrile solution of  
8-chloro-1-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazoline-9(1H)-one (200mg, 0.85mmol), then sodium cyanoborohydride (133mg, 2.11mmol) and acetic acid (0.1mL, 1.69mmol) were added to the reaction mixture. The mixture was stirred at room temperature over  
15 night. The reaction mixture was extracted with ethyl acetate and washed with saturated sodium hydrogen carbonate aqueous solution and brine. The organic layer was dried over MgSO<sub>4</sub> and the solvent was removed in vacuo. The residue was purified by silica gel chromatography eluting with chloroform and methanol (100:5) to give 5-chloro-2-[3-(4-phenyl-1-piperidyl)propyl]-4(3H)-quinazolinone (96.6mg, 0.25mmol, 30%) as colorless  
20 solid.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.88 (2H, m), 2.00 (2H, m), 2.25 (2H, m), 2.28 (5H, m),  
2.60 (2H, m), 2.86 (2H, m), 3.19 (2H, m), 7.33-7.41 (6H, m), and 7.53 (2H, m).

Mass (m/z): 382 (M<sup>+</sup>+1)

### 25 Example 3

4-Cyano-4-phenylpiperidine hydrochloride (452mg, 2.03mmol) was added to the 10% aqueous acetonitrile solution of  
8-chloro-1-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazoline-9(1H)-one (160mg, 0.676mmol), then sodium cyanoborohydride (42.4mg, 0.676mmol) and acetic acid (46mL) were added to  
30 the reaction mixture. The reaction mixture was stirred at room temperature for 4 hours. The mixture was extracted with ethyl acetate and washed with saturated sodium hydrogen carbonate aqueous solution and brine. The organic layer was dried over magnesium sulfate and the solvent was removed in vacuo. The residue was purified by preparative TLC, and recrystallized from methanol to give  
35 5-chloro-2-[3-(4-cyano-4-phenyl-1-piperidyl)propyl]-4(3H)-quinazolinone (22mg, 0.055mmol, 8%) as colorless powder.



<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 2.01(2H, quint, J= 5.5Hz), 2.12 (2H, m), 2.73-2.67 (6H, m),  
2.92 (2H, m), 3.22 (2H, m), 7.43-7.48(4H, m), 7.54(2H, m) and 7.77 (2H, m)  
Mass (m/z): 407 (M<sup>+</sup>+1)

#### 5 Example 4

4-Hydroxy-4-phenylpiperidine hydrochloride(592mg, 3.34mmol) was added to the  
10% aqueous acetonitrile solution of  
8-chloro-1-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazoline-9(1H)-one (395mg, 3.34mmol),  
then sodium cyanoborohydride (157mg, 2.5mmol) and acetic acid (0.15mL) were added to  
10 the reaction mixture. The reaction mixture was stirred at room temperature for 4 hours.  
The mixture was extracted with ethyl acetate and washed with saturated sodium hydrogen  
carbonate aqueous solution and brine. The organic layer was dried over magnesium  
sulfate and the solvent was removed in vacuo. The residue was purified by silica gel  
chromatography eluting with chloroform and methanol (100:5-50:50), and the obtained  
15 colorless solid was washed with ether to give  
5-chloro-2-[3-(4-hydroxy-4-phenyl-1-piperidyl)propyl]-4(3H)-quinazolinone (190mg,  
0.48mmol, 29%) as colorless powder.  
<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.82(2H, d, J= 5.5Hz), 2.01 (2H, m), 2.65-2.77 (6H, m),  
2.90 (2H, m), 3.00 (2H, d, J=9.5 Hz), 7.30 (1H, dm, J=8.7Hz), 7.43-7.48(3H, m),  
20 7.53(2H, m) and 7.71 (2H, dm, J=7.3 Hz)  
Mass (m/z): 398 (M<sup>+</sup>+1)

#### Example 5

4-Amino-4-phenylpiperidine (150mg, 0.85mmol) was added to 10% aqueous  
25 acetonitrile solution of  
8-chloro-1-hydroxy-2,3-dihydropyrrolo[2,1-b]quinazoline-9(1H)-one (181mg, 0.77mmol).  
NaBH<sub>3</sub>CN (64.1mg, 1.02mmol) and AcOH (0.146mL, 2.55mmol) were added to the  
mixture, and the mixture was stirred at room temperature for 4 hours. The reaction  
mixture was extracted with AcOEt, washed with saturated sodium hydrogen carbonate  
30 aqueous solution. Residual solid was purified by preparative TLC (chloroform/methanol  
75:25) to give 2-[3-(4-amino-4-phenyl-1-piperidyl)propyl]-5-chloro-4(3H)-quinazolinone  
(3.5mg, 0.008mmol, 1%) as colorless powder.  
<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.86 (2H, m), 1.97 (2H, m), 2.58 (4H, m), 2.74 (4H, m),  
2.86 (2H, m), 7.25 (1H, m), 7.38 (3H, m), 7.52 (2H, m), and 7.63 (2H, d, J=7.8  
35 Hz).  
Mass (m/z): 397 (M<sup>+</sup>+1)

Example 6

To a solution of 2-[4-(1-phenyl-4-piperidyl)-butanoylamino]benzamide in 1,4-dioxane (6 mL) was added 1N aqueous NaOH (6 mL). The mixture was stirred for 1 hour at room temperature, then H<sub>2</sub>O was added and neutralized with 1N aqueous HCl. A white precipitate was filtered, washed with Et<sub>2</sub>O and dried at 40 °C to give 2-[3-(1-phenyl-4-piperidyl)propyl]-4(3H)-quinazolinone (75 mg, 0.21 mmol, 79%) as a pale yellow powder.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.29-1.55 (5H, m), 1.84 (2H, d, J=10.6 Hz), 1.89-2.04 (2H, m), 2.68 (2H, t, J=10.0 Hz), 2.80 (2H, t, J=7.7 Hz), 3.66 (2H, d, 12.8 Hz), 6.82 (1H, t, J=7.0 Hz), 6.93 (2H, d, J=6.9 Hz), 7.15-7.30 (2H, m), 7.47 (1H, t, J=8.1 Hz), 7.66-7.85 (2H, m), 8.29 (1H, d, J=8.1 Hz), 11.36 (1H, s)

Mass: 348 (M<sup>+</sup>)

Example 7

A mixture of 3-nitroisatoic anhydride (0.11 g) and 4-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)butanimidamide (154 mg) in pyridine was refluxed for 24 hours. The mixture was diluted with water and extracted with dichloromethane three times. The combined extracts were dried over magnesium sulfate, concentrated and co-evaporated with toluene twice. The residue was purified by preparative thin layer chromatography on silica gel using 10% methanol in dichloromethane as an eluent to give 8-nitro-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone as a yellow powder.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 1.80-2.10 (2H, m), 2.40-3.30 (10H, m), 6.02 (1H, s), 7.10-8.60 (8H, m).

Mass (ESI): 391.2 (M<sup>+</sup>+H)

Example 8

Under a nitrogen atmosphere, triethylamine (1.39 mL, 10.0 mmol) was added to a solution of 2-[(4-bromobutanoyl)amino]benzamide (285 mg, 1.00 mmol) and 4-phenyl-4-piperidinol (266 mg, 1.50 mmol) in N,N-dimethylformamide (3 mL) at 0 °C. The mixture was allowed to warm to room temperature and stirred for 13 hours. The reaction was quenched with water, and the product was extracted with chloroform. The organic layer was washed with water and dried over sodium sulfate. The crude 2-[[4-(4-hydroxy-4-phenyl-1-piperidyl)butanoyl]amino]benzamide was dissolved in dioxane (3 mL). An aqueous solution of sodium hydroxide (1M, 3 mL) was added to the

solution at room temperature, and the mixture was stirred at that temperature for 3 hour. The organic materials were extracted with chloroform, and the organic layer was washed with water and dried over sodium sulfate. Recrystallization of the crude product from chloroform-methanol gave

- 5 2-[3-(4-hydroxy-4-phenyl-1-piperidyl)propyl]-4(3H)-quinazolinone (223 mg, 61.4%).  
<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 1.7-1.9 (4H, m), 2.00 (2H, quint., J=5.4 Hz), 2.6-2.8 (5H, m), 2.9-3.1 (4H, m), 7.29 (2H, t, J=6.2 Hz), 7.42 (3H, t, J=7.4 Hz), 7.64 (1H, t, J=6.8 Hz), 7.73 (2H, d, J=8.1 Hz), 8.28 (1H, d, J=7.9 Hz)  
 Mass (APCI): 364.00 (M<sup>+</sup>+H)

10

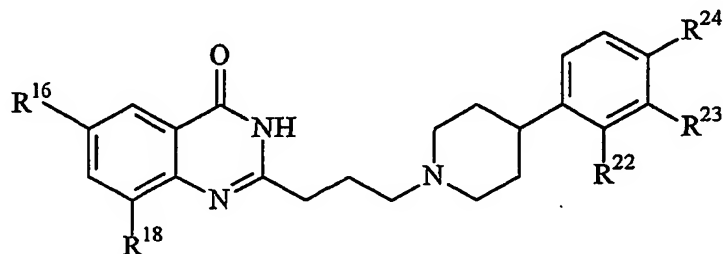
#### Example 9

- 2-{[4-(4-Phenyl-3,6-dihydro-1(2H)-pyridinyl)butanoyl]amino}benzamide (475 mg, 1.31 mmol) was dissolved in dioxane (5 mL). An aqueous solution of sodium hydroxide (1M, 3.92 mL) was added to the solution at room temperature, and the mixture was stirred  
 15 at that temperature for 15 hours. The organic materials were extracted with chloroform, and the organic layer was washed with water and dried over sodium sulfate. Recrystallization of the crude product from chloroform-methanol gave  
 2-{3-[4-phenyl-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone (329 mg, 72.9 %).  
 20 <sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 2.05 (2H, quint., J=6.0 Hz), 2.66 (2H, t, J=6.0 Hz), 2.81-2.94 (4H, m), 3.31 (2H, d, J=3.2 Hz), 6.12 (1H, t, J=2.9 Hz), 7.21-7.49 (7H, m), 7.61-7.72 (2H, m), 8.23 (1H, d, J=6.6 Hz)  
 Mass (APCI): 346.20 (M<sup>+</sup>+H)

#### 25 Example 10

The following compounds are prepared in a similar manner to that of Example 9. If necessary, the starting compounds of them were prepared in similar manners of Preparation 17, Preparation 20 and preparation 23-(2)

30



35

| No. | R <sup>16</sup> | R <sup>18</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup>    |  |
|-----|-----------------|-----------------|-----------------|-----------------|--------------------|--|
| (1) | H               | H               | H               | H               | OEt                | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.41 (3H, t, J=7.0 Hz), 1.8-2.1 (4H, m), 2.1-2.4 (4H, m), 2.4-2.6 (3H, m), 2.9-3.0 (2H, m), 3.19 (2H, br d, J=7.7 Hz), 4.03 (2H, q, J=7.0 Hz), 6.89 (2H, d, J=8.7 Hz), 7.2-7.5 (4H, m), 7.5-7.8 (2H, m), 8.29 (1H, d, J=8.0 Hz)<br>Mass (API-ES): 392.4 (M <sup>+</sup> +H)  |
| (2) | H               | H               | H               | H               | SMe                | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.85 (2H, br d, J=8.7 Hz), 1.96 (2H, quint., J=5.4 Hz), 2.1-2.4 (4H, m), 2.48 (3H, s), 2.5-2.6 (3H, m), 2.9-3.0 (2H, m), 3.20 (2H, br d, J=6.8 Hz), 7.26 (2H, d, J=8.4 Hz), 7.36 (2H, d, J=8.5 Hz), 7.39 (1H, t, J=8.2 Hz), 7.6-7.8 (2H, m), 8.29 (1H, d, J=8.0 Hz).<br>MS (APCI): 394.13 (M <sup>+</sup> +H)      |
| (3) | H               | H               | H               | H               | OCF <sub>3</sub>   | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.86 (2H, br d, J=9.9 Hz), 1.99 (2H, quint., J=5.6 Hz), 2.2-2.4 (4H, m), 2.5-2.7 (3H, m), 2.9-3.0 (2H, m), 3.22 (2H, br d, J=9.0 Hz), 7.20 (2H, d, J=7.9 Hz), 7.4-7.5 (3H, m), 7.63 (1H, d, J=6.8 Hz), 7.68 (1H, t, J=6.8 Hz), 8.29 (1H, d, J=7.9 Hz), 14.10 (1H, br)<br>Mass (APCI): 432.07 (M <sup>+</sup> +H)   |
| (4) | H               | H               | H               | H               | Et                 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.24 (3H, t, J=7.6 Hz), 1.8-2.1 (4H, m), 2.2-2.4 (4H, m), 2.4-2.7 (5H, m), 2.9-3.0 (2H, m), 3.1-3.3 (2H, m), 7.19 (2H, d, J=8.2 Hz), 7.34 (2H, d, J=8.1 Hz), 7.42 (1H, t), 7.6-7.8 (2H, m), 8.2-8.4 (1H, m)<br>Mass (API): 376.4 (M <sup>+</sup> +H)   |
| (5) | H               | H               | H               | H               | N(Me) <sub>2</sub> | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.7-2.1 (4H, m), 2.1-2.3 (4H, m), 2.3-2.6 (3H, m), 2.9-3.0 (8H, m), 3.18 (2H, br d, J=5.9 Hz), 7.77 (2H, d, J=8.8 Hz), 7.30 (2H, d, J=8.7 Hz), 7.67 (1H, t), 7.6-7.7 (2H, m), 8.30 (1H, d, J=6.9 Hz)<br>Mass (APCI): 391.13 (M <sup>+</sup> +H)  |
| (6) | H               | H               | H               | H               | Ph                 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.4-1.7 (4H, m), 1.8-2.0 (4H, m), 2.3-2.5 (3H, m), 2.68 (2H, t, J=6.9 Hz), 2.97 (2H, br d, J=10.9 Hz), 7.20 (2H, d, J=8.2 Hz), 7.3-7.7 (9H, m), 7.77 (1H, t, J=6.9 Hz), 8.12 (1H, d, J=7.9 Hz), 12.43 (1H, br s)<br>Mass (APCI): 424.20 (M <sup>+</sup> +H)  |
| (7) | H               | H               | H               | H               | OPh                | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.8-2.0 (4H, m), 2.3-2.5 (3H, m), 2.67 (2H, t, J=7.1 Hz), 2.95 (2H, br d, J=11.0 Hz), 6.90 (2H, d, J=8.6 Hz), 6.97 (2H, d, J=7.5 Hz), 7.1-7.2 (3H, m), 7.3-7.5 (3H, m), 7.59 (1H, d), 7.76 (1H, t, J=6.8 Hz), 8.10 (1H, d, J=8.0 Hz), 12.43 (1H, br s)<br>Mass (API): 440.4 (M <sup>+</sup> +H) |

| No.  | R <sup>16</sup> | R <sup>18</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup> |  |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (8)  | H               | H               | H               | H               | Ac              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.4-1.7 (4H, m), 1.8-2.1 (4H, m), 2.3-2.5 (3H, m), 2.55 (3H, s), 2.67 (2H, t, J=6.9 Hz), 2.96 (2H, br d, J=11.0 Hz), 7.26 (2H, d, J=8.3 Hz), 7.46 (1H, t, J=6.9 Hz), 7.59 (1H, d, J=7.6 Hz), 7.76 (1H, t, J=7.1 Hz), 7.86 (2H, d, J=8.3 Hz), 8.11 (1H, d, J=7.9 Hz), 12.42 (1H, br s)<br>Mass (APCI): 390.07 (M <sup>+</sup> +H) |
| (9)  | H               | H               | H               | H               | H               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.88 (2H, d, J=9.5 Hz), 1.99 (2H, quint., J=5.5 Hz), 2.1-2.5 (4H, m), 2.5-2.7 (3H, m), 2.9-3.0 (2H, m), 3.21 (2H, br d, J=7.9 Hz), 7.1-7.5 (6H, m), 7.63 (1H, d, J=6.9 Hz), 7.71 (1H, t, J=6.8 Hz), 8.30 (1H, d, J=7.9 Hz)<br>Mass (APCI): 348.20 (M <sup>+</sup> +H)  |
| (10) | H               | H               | H               | H               | Me              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.86 (2H, br d, J=7.8 Hz), 1.94 (2H, quint., J=5.9 Hz), 2.1-2.4 (4H, m), 2.34 (3H, s), 2.5-2.7 (3H, m), 2.9-3.0 (2H, m), 3.20 (2H, br d, J=6.5 Hz), 7.16 (2H, d, J=7.9 Hz), 7.31 (2H, d, J=8.1 Hz), 7.42 (1H, t, J=8.1 Hz), 7.6-7.7 (2H, m), 8.2-8.3 (1H, m)<br>Mass (API): 362.4 (M <sup>+</sup> +H)                              |
| (11) | H               | H               | H               | H               | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.87 (2H, br d, J=11.1 Hz), 1.93 (2H, quint., J=5.7 Hz), 2.1-2.5 (4H, m), 2.5-2.8 (3H, m), 2.9-3.0 (2H, m), 3.23 (2H, br d, J=10.4 Hz), 7.43 (1H, t, J=8.0 Hz), 7.5-7.8 (6H, m), 8.2-8.3 (1H, m), 14.05 (1H, br)<br>Mass (APCI): 416.00 (M <sup>+</sup> +H)  |
| (12) | H               | H               | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.8-2.1 (4H, m), 2.3-2.4 (3H, m), 2.67 (2H, t, J=7.1 Hz), 2.94 (2H, d, J=11.2 Hz), 7.0-7.2 (4H, m), 7.46 (1H, t, J=8.0 Hz), 7.58 (1H, d, J=7.5 Hz), 7.7-7.8 (1H, m), 8.11 (1H, dd, J=7.9, 1.2 Hz)<br>Mass: 365.9 (M <sup>+</sup> )  |
| (13) | H               | H               | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.8-2.1 (4H, m), 2.25-2.45 (3H, m), 2.66 (2H, t, J=7.1 Hz), 2.93 (2H, d, J=11.2 Hz), 3.71 (3H, s), 6.81 (2H, d, J=8.7 Hz), 7.02 (2H, d, J=8.7 Hz), 7.45 (1H, t, J=8.0 Hz), 7.58 (1H, d, J=7.5 Hz), 7.7-7.8 (1H, m), 8.10 (1H, dd, J=7.9, 1.2 Hz)<br>Mass: 377.8 (M <sup>+</sup> )                               |
| (14) | H               | Cl              | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.8-2.0 (3H, m), 2.3-2.6 (4H, m), 2.6-2.8 (2H, m), 2.8-3.0 (2H, m), 6.9-7.2 (4H, m), 7.34 (1H, t, J=8.0 Hz), 7.83 (1H, dd, J=8.0, 1.4 Hz), 8.04 (1H, dd, J=8.0, 1.4 Hz)<br>Mass: 400 (M <sup>+</sup> +H)  |

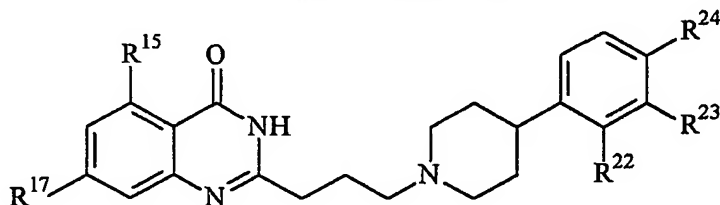
| No.  | R <sup>16</sup> | R <sup>18</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup> |   |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|---|
| (15) | H               | Cl              | H               | H               | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.62 (3H, s), 1.8-2.0 (3H, m), 2.3-2.6 (4H, m), 2.6-2.8 (2H, m), 2.8-3.0 (2H, m), 6.9-7.2 (4H, m), 7.31 (1H, t, J = 8.0Hz), 7.81 (1H, dd, J = 8.0, 1.4Hz), 8.01 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 396 (M <sup>+</sup> +H)                                      |
| (16) | H               | Cl              | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.8-2.0 (3H, m), 2.3-2.6 (4H, m), 2.6-2.8 (2H, m), 2.8-3.0 (2H, m), 3.70 (3H, s), 6.80 (2H, d, J = 8Hz), 6.97 (2H, d, J = 8Hz), 7.43 (1H, t, J = 8Hz), 7.91 (1H, dd, J = 8.0, 1.4Hz), 8.07 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 412 (M <sup>+</sup> +H)           |
| (17) | H               | Cl              | H               | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.8-2.0 (3H, m), 2.3-2.6 (4H, m), 2.6-2.8 (2H, m), 2.8-3.0 (2H, m), 7.0-7.3 (5H, m), 7.42 (1H, t, J = 8Hz), 7.91 (1H, dd, J = 8.0, 1.4Hz), 8.07 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 382 (M <sup>+</sup> +H)  |
| (18) | H               | Me              | H               | H               | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.7-2.0 (3H, m), 2.24 (3H, s), 2.4-2.6 (2H, m), 2.67 (3H, s), 2.5-2.8 (2H, m), 2.8-3.0 (2H, m), 6.96 (2H, d, 8Hz), 7.05 (2H, d, J = 8Hz), 7.30 (1H, t, J = 8Hz), 7.60 (1H, dd, J = 7.6, 1.4Hz), 7.93 (1H, dd, J = 7.6, 1.4Hz)<br>Mass: 376 (M <sup>+</sup> +H) |
| (19) | H               | Me              | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (3H, m), 1.7-2.1 (4H, m), 2.2-2.4 (4H, m), 2.51 (3H, s), 2.6-2.8 (2H, m), 2.9-3.1 (2H, m), 3.72 (3H, s), 6.80 (2H, d, 8Hz), 7.01 (2H, d, J = 8Hz), 7.32 (1H, t, J = 8Hz), 7.62 (1H, dd, J = 7.6, 1.4Hz), 7.94 (1H, dd, J = 7.6, 1.4Hz)<br>Mass: 392 (M <sup>+</sup> +H) |
| (20) | H               | Me              | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-1.7 (4H, m), 1.8-2.1 (3H, m), 2.3-2.5 (4H, m), 2.51 (3H, s), 2.6-2.8 (2H, m), 2.8-3.1 (2H, m), 3.72 (3H, s), 7.0-7.3 (4H, m), 7.61 (1H, t, J = 8Hz), 7.93 (1H, dd, J = 7.6, 1.4Hz), 7.95 (1H, dd, J = 7.6, 1.4Hz)<br>Mass: 380 (M <sup>+</sup> +H)                          |
| (21) | H               | OMe             | H               | H               | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-2.1 (7H, m), 2.0-3.0 (8H, m), 2.50 (3H, s), 4.08 (3H, s), 6.9-7.8 (7H, m)<br>Mass: 392 (M <sup>+</sup> +H)  |
| (22) | H               | OMe             | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-2.0 (7H, m), 2.2-3.0 (8H, m), 2.49 (3H, s), 3.90 (3H, s), 6.9-7.8 (7H, m)<br>Mass: 396 (M <sup>+</sup> +H)  |

| No.  | R <sup>16</sup> | R <sup>18</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup> |   |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|---|
| (23) | H               | OMe             | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.3-2.0 (7H, m), 2.1-3.0 (8H, m), 3.49 (3H, s), 3.71 (3H, s), 4.00 (3H, s), 6.81 (2H, d, J = 8Hz), 7.05 (2H, d, J = 8Hz), 7.2-7.8 (3H, m)<br>Mass: 408 (M <sup>+</sup> +H)  |
| (24) | Cl              | H               | H               | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.2-1.7 (4H, m), 1.8-2.0 (4H, m), 2.2-2.5 (3H, m), 2.6-3.0 (4H, m), 6.9-7.3 (5H, m), 7.61 (1H, d, J = 8Hz), 7.79 (1H, d, J = 8Hz), 8.05 (1H, s)<br>Mass: 382 (M <sup>+</sup> +H)  |
| (25) | Cl              | H               | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.2-1.7 (4H, m), 1.8-2.0 (4H, m), 2.2-2.5 (3H, m), 2.6-3.0 (4H, m), 3.70 (3H, s), 6.79 (2H, d, J = 8Hz), 6.96 (2H, d, J = 8Hz), 7.60 (1H, d, J = 8Hz), 7.79 (1H, d, J = 8Hz), 8.00 (1H, s)<br>Mass: 412 (M <sup>+</sup> +H) |
| (26) | Cl              | H               | H               | H               | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.2-1.7 (4H, m), 1.8-2.0 (4H, m), 2.2-2.5 (3H, m), 2.34 (3H, s), 2.6-3.0 (4H, m), 6.95 (2H, d, J = 8Hz), 7.05 (2H, d, J = 8Hz), 7.55 (1H, d, J = 8Hz), 7.75 (1H, d, J = 8Hz), 8.00 (1H, s)<br>Mass: 396 (M <sup>+</sup> +H) |
| (27) | Cl              | Cl              | H               | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.2-2.0 (8H, m), 2.2-2.4 (3H, m), 2.5-3.0 (4H, m), 7.0-7.5 (5H, m), 8.0-8.2 (2H, m)<br>Mass: 417(M <sup>+</sup> +H)   |

**Example 11**

The following compounds are prepared in a similar manner to that of Example 9.  
If necessary, the starting compounds of them were prepared in similar manners of  
Preparation 17, Preparation 20 and preparation 23-(2)

10



| No. | R <sup>15</sup> | R <sup>17</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup> |  |
|-----|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (1) | Cl              | H               | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.2-2.0 (8H, m), 2.2-2.4 (3H, m), 2.5-2.8 (2H, m), 2.8-3.0 (2H, m), 3.70 (3H, s), 6.80 (2H, d, J = 8.0Hz), 7.01 (2H, d, J = 8.0Hz), 7.3-7.8 (3H, m)<br>Mass: 412 (M <sup>+</sup> +H) |

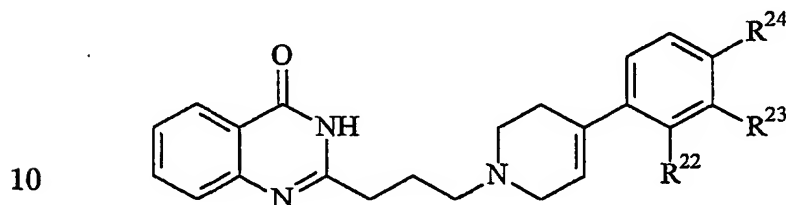
| No. | R <sup>15</sup> | R <sup>17</sup> | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup> |  |
|-----|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (2) | Cl              | H               | H               | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.2-2.0 (8H, m), 2.2-2.4 (3H, m), 2.5-2.8 (2H, m), 2.8-3.0 (2H, m), 7.0-7.7 (8H, m)<br>Mass: 382 (M <sup>+</sup> +H)   |
| (3) | F               | H               | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.1 (4H, m), 2.1-2.3 (4H, m), 2.4-2.6 (3H, m), 2.8-3.0 (2H, m), 3.19 (2H, br d, J=6.2 Hz), 3.80 (3H, s), 6.89 (2H, d, J=8.7 Hz), 7.05 (1H, dd, J=9.5, 8.4 Hz), 7.32 (2H, d, J=8.7 Hz), 7.41 (1H, d, J=8.2 Hz), 7.62 (1H, dt, J=8.1, 5.5 Hz)<br>Mass (API): 396.3 (M <sup>+</sup> +H) |
| (4) | F               | H               | H               | H               | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.84 (2H, br d, J=8.2 Hz), 1.97 (2H, quint., J=5.7 Hz), 2.1-2.4 (4H, m), 2.4-2.7 (3H, m), 2.8-3.0 (2H, m), 3.21 (2H, br d, J=6.5 Hz), 6.9-7.1 (3H, m), 7.3-7.5 (3H, m), 7.62 (1H, dt, J=8.2, 5.5 Hz)<br>Mass (API): 384.3 (M <sup>+</sup> +H)  |

Example 12

The following compounds are prepared in a similar manner to that of Example 9.

If necessary, the starting compounds of them were prepared in similar manners of

5 Preparation 17 and Preparation 20.



| No. | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup> |  |
|-----|-----------------|-----------------|-----------------|--|
| (1) | F               | H               | H               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=6.4 Hz), 2.67 (2H, t, J=6.2 Hz), 2.7-3.0 (6H, m), 3.31 (2H, q, J=3.2 Hz), 6.02 (1H, m), 7.0-7.5 (5H, m), 7.6-7.8 (2H, m), 8.25 (1H, d, J=7.8 Hz), 12.64 (1H, br)<br>Mass (API) 364.3 (M <sup>+</sup> +H)                         |
| (2) | H               | F               | H               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=7.1 Hz), 2.66 (2H, t, J=6.0 Hz), 2.7-3.0 (6H, m), 3.30 (2H, q, J=3.2 Hz), 6.13 (1H, m), 6.95 (1H, t, J=8.2 Hz), 7.1-7.5 (4H, m), 7.6-7.8 (2H, m), 8.23 (1H, d, J=7.9 Hz), 12.55(1H, br)<br>Mass (API): 364.4 (M <sup>+</sup> +H) |



| No. | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup>    |  |
|-----|-----------------|-----------------|--------------------|--|
| (3) | OMe             | H               | H                  | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.04 (2H, quint., J=6.2 Hz), 2.66 (2H, t, J=6.2 Hz), 2.7-3.0 (6H, m), 3.29 (2H, q, J=2.6 Hz), 3.84 (3H, s), 5.83 (1H, m), 6.88 (1H, d, J=8.2 Hz), 6.95 (1H, t, J=7.4 Hz), 7.2-7.3 (2H, m), 7.42 (1H, t, J=7.3 Hz), 7.6-7.8 (2H, m), 8.28 (1H, d, J=11.2 Hz)<br>Mass (APCI): 376.13 (M <sup>+</sup> +H)                                     |
| (4) | H               | OMe             | H                  | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=7.2 Hz), 2.66 (2H, t, J=6.0 Hz), 2.7-3.0 (6H, m), 3.30 (2H, q, J=1.6 Hz), 3.84 (3H, s), 6.10 (1H, m), 6.82 (1H, dd, J=8.1, 2.6 Hz), 7.00 (1H, t, J=2.3 Hz), 7.06 (1H, d, J=7.9 Hz), 7.26 (1H, t, J=7.9 Hz), 7.41 (1H, t, J=7.3 Hz), 7.6-7.8 (2H, m), 8.23 (1H, d, J=7.9 Hz)<br>Mass (APCI): 376.07 (M <sup>+</sup> +H) |
| (5) | H               | H               | OEt                | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.42 (3H, t, J=7.0 Hz), 2.04 (2H, quint., J=6.0 Hz), 2.65 (2H, t, J=6.0 Hz), 2.7-3.0 (4H, m), 3.29 (2H, d, J=3.2 Hz), 4.05 (2H, q, J=7.0 Hz), 6.01 (1H, br s), 6.87 (2H, d, J=8.8 Hz), 7.3-7.5 (3H, m), 7.6-7.8 (2H, m), 8.23 (1H, d, J=7.9 Hz)<br>Mass (API-ES): 390.3 (M <sup>+</sup> +H)  |
| (6) | H               | H               | SMe                | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=6.1 Hz), 2.49 (3H, s), 2.65 (2H, t, J=6.0 Hz), 2.7-3.0 (6H, m), 3.30 (2H, d, J=3.3 Hz), 6.08 (1H, t, J=3.5 Hz), 7.24 (2H, d, J=7.5 Hz), 7.3-7.5 (3H, m), 7.6-7.8 (2H, m), 8.23 (1H, dd, J=7.9, 1.0 Hz)<br>Mass (API-ES): 392.3 (M <sup>+</sup> +H)   |
| (7) | H               | H               | OCF <sub>3</sub>   | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=5.9 Hz), 2.67 (2H, t, J=5.9 Hz), 2.7-3.0 (6H, m), 3.31 (2H, q, J=3.3 Hz), 6.08 (1H, t, J=3.5 Hz), 7.19 (2H, d, J=8.0 Hz), 7.42 (1H, t, J=6.6 Hz), 7.48 (2H, d, J=8.7 Hz), 7.6-7.8 (2H, m), 8.23 (1H, dd, J=8.0, 0.9 Hz)<br>MS (APCI): 429.87 (M <sup>+</sup> +H)   |
| (8) | H               | H               | Et                 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.24 (3H, t, J=7.6 Hz), 2.05 (2H, quint., J=6.1 Hz), 2.5-3.0 (10H, m), 3.29 (2H, q, J=3.3 Hz), 6.06 (1H, m), 7.17 (2H, d, J=8.4 Hz), 7.3-7.5 (3H, m), 7.6-7.8 (2H, m), 8.23 (1H, d, J=8.0 Hz)<br>MS (APCI) 373.73 (M <sup>+</sup> +H)  |
| (9) | H               | H               | N(Me) <sub>2</sub> | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.04 (2H, quint., J=6.3 Hz), 2.64 (2H, t, J=6.0 Hz), 2.7-2.9 (4H, m), 2.95 (6H, s), 3.61 (2H, m), 5.98 (1H, t, J=3.5 Hz), 6.72 (2H, d, J=8.9 Hz), 7.3-7.5 (3H, m), 7.6-7.8 (2H, m), 8.24 (1H, d, J=7.9 Hz)<br>MS (API-ES): 389.4 (M <sup>+</sup> +H)   |

| No.  | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup> |   |
|------|-----------------|-----------------|-----------------|---|
| (10) | H               | H               | t-Bu            | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.33 (9H, s), 2.04 (2H, quint., J=6.1 Hz), 2.65 (2H, t, J=6.0 Hz), 2.8-3.0 (4H, m), 3.30 (2H, q, J=3.2 Hz), 6.08 (1H, br s), 7.3-7.5 (5H, m), 7.63 (1H, d, J=6.8 Hz), 7.71 (1H, t, J=6.7 Hz), 8.23 (1H, d, J=7.9 Hz)<br>MS (APCI): 402.00 (M <sup>+</sup> +H)   |
| (11) | H               | H               | Ph              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.97 (2H, quint., J=6.0 Hz), 2.4-2.5 (4H, m), 2.6-2.8 (4H, m), 3.12 (2H, br s), 6.20 (1H, m), 7.3-7.5 (6H, m), 7.5-7.8 (6H, m), 8.06 (1H, d, J=7.9 Hz), 12.49 (1H, br s)<br>MS (APCI): 422.07 (M <sup>+</sup> +H)   |
| (12) | H               | H               | OPh             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.96 (2H, quint., J=6.9 Hz), 2.4-2.5 (4H, m), 2.6-2.7 (4H, m), 3.08 (2H, br s), 6.07 (1H, br s), 6.95 (2H, d, J=8.7 Hz), 7.01 (2H, d, J=8.3 Hz), 7.14 (1H, t, J=7.4 Hz), 7.39 (2H, t, J=7.5 Hz), 7.40 (2H, d, J=8.8 Hz), 7.59 (1H, d, J=7.6 Hz), 7.77 (1H, t), 8.04 (1H, d, J=7.8 Hz), 12.22 (1H, br s)<br>MS (API-ES): 438.3 (M <sup>+</sup> +H) |
| (13) | H               | H               | Ac              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.06 (2H, quint., J=6.1 Hz), 2.61 (3H, s), 2.68 (2H, t, J=6.0 Hz), 2.8-3.0 (4H, m), 3.33 (2H, d, J=3.2 Hz), 6.24 (1H, t, J=3.6 Hz), 7.42 (1H, t), 7.54 (2H, d, J=8.6 Hz), 7.6-7.8 (2H, m), 7.94 (2H, d, J=8.6 Hz), 8.22 (1H, d, J=7.4 Hz)   |
| (14) | H               | H               | Me              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=6.2 Hz), 2.35 (3H, s), 2.65 (2H, t, J=6.0 Hz), 2.78-2.93 (6H, m), 3.30 (2H, d, J=3.2 Hz), 6.06 (1H, m), 7.15 (2H, d, J=8.1 Hz), 7.35 (2H, d, J=8.2 Hz), 7.43 (1H, d, J=6.5 Hz), 7.65 (1H, t, J=6.9 Hz), 7.71 (1H, t, J=8.2 Hz), 8.24 (1H, dd, J=8.0, 1.2 Hz)<br>MS (APCI): 360.13 (M <sup>+</sup> +H)                           |
| (15) | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.04 (2H, quint., J=6.0 Hz), 2.65 (2H, t, J=6.0 Hz), 2.79-2.93 (6H, m), 3.29 (2H, d, J=3.2 Hz), 3.82 (3H, s), 6.01 (1H, m), 6.88 (2H, d, J=8.8 Hz), 7.37-7.46 (3H, m), 7.63 (1H, d, J=7.0 Hz), 7.71 (1H, t, J=7.8 Hz), 8.23 (1H, d, J=7.8 Hz)<br>MS (APCI): 376.07 (M <sup>+</sup> +H)  |
| (16) | H               | H               | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=6.1 Hz), 2.66 (2H, t, J=5.9 Hz), 2.79-2.93 (6H, m), 3.30 (2H, d, J=3.0 Hz), 6.03 (1H, m), 7.03 (2H, t, J=8.7 Hz), 7.37-7.46 (3H, m), 7.65 (1H, t, J=6.9 Hz), 7.71 (1H, t, J=7.5 Hz), 8.23 (1H, d, J=6.9 Hz)<br>MS (APCI): 364.00 (M <sup>+</sup> +H)  |

| No.  | R <sup>22</sup> | R <sup>23</sup> | R <sup>24</sup>    |   |
|------|-----------------|-----------------|--------------------|---|
| (17) | H               | H               | CF <sub>3</sub>    | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.06 (2H, quint., J=6.1 Hz), 2.68 (2H, t, J=5.9 Hz), 2.83-2.94 (6H, m), 3.33 (2H, d, J=3.1 Hz), 6.18 (1H, m), 7.41 (1H, t, J=7.3 Hz), 7.53-7.76 (6H, m), 8.23 (1H, d, J=6.6 Hz)<br>MS (APCI): 413.93 (M <sup>+</sup> +H)                      |
| (18) | H               | H               | CN                 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.03 (2H, quint., J=6.0 Hz), 2.68 (2H, t, J=5.9 Hz), 2.78-2.94 (6H, m), 3.33 (2H, q, J=3.3 Hz), 6.21 (1H, m), 7.43 (1H, t, J=8.1 Hz), 7.51-7.72 (6H, m), 8.22 (1H, dd, J=7.8, 1.1 Hz)<br>MS (APCI): 370.93 (M <sup>+</sup> +H)                |
| (19) | H               | H               | CH <sub>2</sub> OH | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , δ): 1.9-2.1 (2H, m), 2.3-2.8 (10H, m), 3.07 (2H, d, J=2.8 Hz), 4.47 (2H, s), 6.08 (1H, s), 7.25 (2H, d, J=8.4 Hz), 7.34 (2H, d, J=8.4 Hz), 7.4-7.5 (1H, m), 7.59 (2H, d, J=7.5 Hz), 7.7-7.8 (1H, m), 8.0-8.1 (1H, m)<br>Mass: 376.0 (M <sup>+</sup> +H) |
| (20) | H               | H               | Cl                 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H, m), 2.3-2.8 (8H, m), 3.0-3.2 (2H, m), 6.12 (1H, m), 7.0-7.8 (8H, m)<br>Mass: 380 (M <sup>+</sup> +H)   |

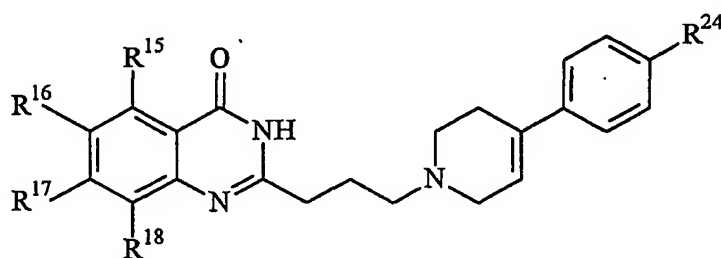
**Example 13**

The following compounds were prepared in a similar manner to that of **Example 9**.

If necessary, the starting compounds of them were prepared in similar manners of

5 **Preparation 17** and **Preparation 20**.

10



20

| No. | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |   |
|-----|-----------------|-----------------|-----------------|-----------------|-----------------|---|
| (1) | Cl              | H               | H               | H               | CN              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): d/ppm 1.94 (2H, quint., J=6.8 Hz), 2.3-2.5 (4H, m), 2.5-2.7 (4H, m), 3.09 (2H, br s), 6.31 (1H, br s), 7.39 (1H, d, J=7.6 Hz), 7.5-7.7 (4H, m), 7.77 (2H, d, J=8.5 Hz), 12.23 (1H, br s)<br>Mass (APCI): 405.00 (M <sup>+</sup> +H) |

| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |   |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|---|
| (2)  | Cl              | H               | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 3.0-3.2 (2H, m), 3.74 (3H, s), 5.97 (1H, m), 6.87 (2H, d, J=8.0 Hz), 7.35 (2H, d, J=8.0 Hz), 7.40 (1H, dd, J=7.6, 1.4 Hz), 7.51 (1H, dd, J=7.6, 1.4 Hz), 7.65 (1H, t, J=7.6 Hz)<br>Mass: 410 (M <sup>+</sup> +H)  |
| (3)  | F               | H               | H               | H               | H               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.04 (2H, quint., J=6.1 Hz), 2.66 (2H, t, J=6.0 Hz), 2.7-3.0 (6H, m), 3.31 (2H, m), 6.10 (1H, m), 7.04 (1H, dd, J=10.5, 8.2 Hz), 7.2-7.5 (6H, m), 7.63 (1H, dt, J=8.1, 5.4 Hz)<br>MS (APCI): 364.07 (M <sup>+</sup> +H)   |
| (4)  | F               | H               | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.03 (2H, quint., J=6.7 Hz), 2.65 (2H, t, J=6.0 Hz), 2.7-2.9 (6H, m), 3.29 (2H, q, J=3.2 Hz), 6.00 (1H, t, J=3.5 Hz), 6.87 (2H, d, J=8.9 Hz), 7.04 (1H, dd, J=10.5, 8.1 Hz), 7.38 (2H, d, J=8.9 Hz), 7.40 (1H, t, J=6.3 Hz), 7.62 (1H, dt, J=8.2, 5.5 Hz)<br>MS (API-ES): 394.4 (M <sup>+</sup> +H) |
| (5)  | F               | H               | H               | H               | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.04 (2H, quint., J=6.0 Hz), 2.66 (2H, t, J=6.0 Hz), 2.7-2.9 (6H, m), 3.29 (2H, d, J=2.9 Hz), 6.03 (1H, m), 6.9-7.1 (3H, m), 7.3-7.5 (3H, m), 7.5-7.7 (1H, m)<br>MS (APCI): 381.87 (M <sup>+</sup> +H)  |
| (6)  | H               | H               | Cl              | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 3.0-3.2 (2H, m), 6.08 (1H, m), 7.1-7.5 (6H, m), 7.65 (1H, d, J=2.0 Hz), 8.02 (1H, d, J=8.0 Hz)<br>Mass: 380 (M <sup>+</sup> +H)   |
| (7)  | H               | Cl              | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.9-3.1 (2H, m), 6.01 (1H, m), 7.0-7.5 (5H, m), 7.60 (1H, d, J=8 Hz), 7.70 (1H, dd, J=8.0, 1.6 Hz), 7.93 (1H, d, 1.6Hz)<br>Mass: 398 (M <sup>+</sup> +H)  |
| (8)  | H               | Cl              | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.9-3.1 (2H, m), 5.94 (1H, m), 6.86 (2H, d, J=8 Hz), 7.28 (2H, d, J=8 Hz), 7.59 (1H, d, J=8 Hz), 7.75 (1H, dd, J=8.0, 1.6 Hz), 7.93 (1H, d, 1.6Hz)<br>Mass: 410 (M <sup>+</sup> +H)   |
| (9)  | H               | Cl              | H               | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.9-3.1 (2H, m), 6.05 (1H, m), 7.1-7.5 (5H, m), 7.61 (1H, d, J=8 Hz), 7.78 (1H, dd, J=8.0, 1.6 Hz), 8.01 (1H, d, 1.6Hz)<br>Mass: 380 (M <sup>+</sup> +H)  |
| (10) | H               | Cl              | H               | Cl              | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 3.0-3.2 (2H, m), 5.99 (1H, m), 7.2-7.4 (5H, m), 7.80 (1H, d, J=1.4 Hz), 8.02 (1H, d, J=1.2 Hz)<br>Mass: 415 (M <sup>+</sup> +H)   |

| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |  |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (11) | H               | Cl              | H               | Cl              | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 3.0-3.2 (2H, m), 3.74 (3H, s), 5.88 (1H, m), 6.85 (2H, d, J = 8Hz), 7.22 (2H, J=8 Hz), 7.88 (1H, d, J=1.5 Hz), 8.11 (1H, d, J=1.5 Hz)<br>Mass: 445 (M <sup>+</sup> +H)     |
| (12) | H               | Cl              | H               | Cl              | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 3.0-3.2 (2H, m), 5.95 (1H, m), 6.9-7.3 (4H, m), 7.86 (1H, d, J=1.5 Hz), 8.00 (1H, d, J=1.5 Hz)<br>Mass: 433 (M <sup>+</sup> +H)  |
| (13) | H               | Cl              | H               | Cl              | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.48 (3H, s), 3.0-3.2 (2H, m), 5.95 (1H, m), 7.0-7.3 (4H, m), 8.01 (1H, d, J=1.5 Hz), 8.06 (1H, d, J=1.5 Hz)<br>Mass: 429 (M <sup>+</sup> +H)                              |
| (14) | H               | F               | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H, m), 2.3-2.9 (8H, m), 3.0-3.2 (2H, m), 6.04 (1H, m), 7.1-7.3 (2H, m), 7.3-7.5 (2H, m), 7.6-7.9 (3H, m)<br>Mass: 382 (M <sup>+</sup> +H)  |
| (15) | H               | F               | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H, m), 2.3-2.8 (8H, m), 3.0-3.2 (2H, m), 3.74 (3H, s), 5.97 (1H, m), 6.87 (2H, d, J=8 Hz), 7.33 (2H, d, J=8 Hz), 7.6-7.9 (3H, m)<br>Mass: 394 (M <sup>+</sup> +H)                                  |
| (16) | H               | F               | H               | H               | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H, m), 2.3-2.8 (8H, m), 3.0-3.2 (2H, m), 6.12 (1H, m), 7.0-7.8 (7H, m)<br>Mass: 398 (M <sup>+</sup> +H)  |
| (17) | H               | Me              | H               | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H, m), 2.32 (3H, s), 2.8-3.8 (10H, m), 6.16 (1H, m), 7.2-7.9 (9H, m)<br>Mass: 360 (M <sup>+</sup> +H)  |
| (18) | H               | Me              | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H, m), 2.51 (3H, s), 2.8-3.8 (10H, m), 6.13 (1H, m), 7.1-7.7 (6H, m), 7.86 (1H, s)<br>Mass: 378 (M <sup>+</sup> +H)  |
| (19) | H               | H               | H               | I               | H               | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.80 - 2.20 (2H, m), 2.30 - 2.90 (8H, m), 3.10 (2H, d, J=3.1 Hz), 6.06 (1H, s), 7.00 - 7.60 (6H, m), 8.03 (1H, dd, J=1.4 Hz, J=7.8 Hz), 8.30 (1H, dd, J=1.4 Hz, J=7.8 Hz)<br>Mass (APCI): 470.20 (M <sup>+</sup> +H) |
| (20) | H               | H               | H               | Br              | H               | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.80 - 2.10 (2H, m), 2.20 - 2.90 (8H, m), 3.10 (2H, d, J=2.7 Hz), 6.07 (1H, s), 7.10 - 7.60 (6H, m), 7.90 - 8.20 (2H, m), 12.42 (1H, brs)<br>Mass (APCI): 424.33 (M <sup>+</sup> +H)                                 |

| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup>    |  |
|------|-----------------|-----------------|-----------------|-----------------|--------------------|--|
| (21) | H               | H               | H               | Et              | H                  | <sup>1</sup> H NMR (DMSO-d <sub>6</sub> , δ): 1.24 (3H, t, J=7.4 Hz), 1.80 - 2.10 (2H, m), 2.20 - 2.80 (8H, m), 3.00 (2H, q, J=7.4 Hz), 6.11 (1H, s), 7.10 - 7.50 (6H, m), 7.63 (1H, dd, J=1.6, 7.3 Hz), 7.91 (1H, dd, J=1.6, 7.9 Hz)<br>Mass (APCI): 373.49 (M <sup>+</sup> +H)   |
| (22) | H               | H               | H               | Cl              | OMe                | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , δ): 1.9-2.1 (2H, m), 2.46 (2H, s), 2.5-2.8 (6H, m), 3.05 (2H, s), 3.74 (3H, s), 5.95 (1H, s), 6.86 (2H, d, J=8.7 Hz), 7.28 (2H, d, J=8.7 Hz), 7.38 (1H, t, J=7.8 Hz), 7.81 (1H, d, J=7.8 Hz), 7.99 (1H, d, J=7.8 Hz)<br>Mass: 410.0 (M <sup>+</sup> +H)  |
| (23) | H               | H               | H               | Cl              | H                  | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , δ): 1.9-2.1 (2H, m), 2.29 (2H, s), 2.45-2.8 (6H, m), 3.07 (2H, d, J=3.1 Hz), 6.06 (1H, s), 7.2-7.4 (6H, m), 7.90 (1H, dd, J=7.8, 1.5 Hz), 7.99 (1H, dd, J=7.8, 1.4 Hz), 12.46 (1H, br s)<br>Mass: 380.1 (M <sup>+</sup> +H)  |
| (24) | H               | H               | H               | Cl              | CF <sub>3</sub>    | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , δ): 1.9-2.1 (2H, m), 2.3-2.5 (2H, m), 2.5-2.8 (6H, m), 3.10 (2H, d, J=2.6 Hz), 6.24 (1H, s), 7.36 (1H, t, J=7.8 Hz), 7.56 (2H, d, J=8.3 Hz), 7.66 (2H, d, J=8.3 Hz), 7.91 (1H, dd, J=7.8, 1.4 Hz), 7.98 (1H, dd, J=7.8, 1.4 Hz)<br>Mass: 448.1 (M <sup>+</sup> +H)   |
| (25) | H               | H               | H               | Cl              | CH <sub>2</sub> OH | <sup>1</sup> H-NMR (DMSO-d <sub>6</sub> , δ): 1.9-2.1 (2H, m), 2.3-2.5 (2H, m), 2.5-2.8 (4H, m), 3.07 (2H, d, J=2.9 Hz), 4.46 (2H, d, J=5.0 Hz), 5.12 (1H, t, J=5.4 Hz), 6.05 (1H, s), 7.24 (2H, d, J=8.4 Hz), 7.31 (2H, d, J=8.4 Hz), 7.38 (1H, t, J=7.9 Hz), 7.90 (1H, dd, J=7.9, 1.4 Hz), 7.99 (1H, dd, J=7.9, 1.4 Hz)<br>Mass: 410.0 (M <sup>+</sup> +H) |
| (26) | H               | H               | H               | Cl              | F                  | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.1 (2H,m), 2.2-2.8 (8H,m), 3.3 (2H, br.s), 6.03 (1H, m), 7.0-7.2 (2H, m), 7.3-7.6 (2H, m), 7.42 (1H, t, J=8.0 Hz), 7.90 (1H,dd, J=8.0, 1.4 Hz), 7.99 (1H,dd, J=8.0, 1.4 Hz)<br>Mass: 398 (M <sup>+</sup> +H)  |
| (27) | H               | H               | H               | Cl              | OMe                | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.1 (2H,m), 2.2-2.8 (8H,m), 3.1 (2H, br.s), 3.74 (3H,s), 5.98 (1H, m), 6.87 (2H, d, J=8.8 Hz), 7.28 (1H t, J=8.2 Hz), 7.29 (2H, d, J=8.8 Hz), 7.79 (1H, dd, J=8.8, 1.4 Hz), 7.96 (1H, dd, J=8.8, 1.4 Hz)<br>Mass: 410 (M <sup>+</sup> +H)  |

| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |  |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (28) | H               | H               | H               | Cl              | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.1 (2H,m), 2.1 (3H, s), 2.2-2.8 (8H,m), 3.1 (2H, br.s), 6.03 (1H, m), 7.11 (2H, d, J=8.8 Hz), 7.22 (2H, d, J=8.8 Hz), 7.29 (1H, t, J=8.8 Hz), 7.81 (1H, dd, J=8.8, 1.4 Hz), 7.96 (1H, dd, J=8.8, 1.4 Hz)<br>Mass: 394 (M <sup>+</sup> +H)             |
| (29) | H               | H               | H               | Cl              | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.1 (2H,m), 2.3-2.8 (8H,m), 3.05 (2H, br.s), 6.13 (1H, m), 7.2-7.5 (5H, m), 7.83 (1H, dd, J=8.0, 1.4 Hz), 7.96 (1H, dd, J=8.0, 1.4 Hz)<br>Mass: 415 (M <sup>+</sup> +H)  |
| (30) | H               | H               | H               | Cl              | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.1 (2H,m), 2.3-2.8 (8H,m), 3.05 (2H, br.s), 6.07 (1H, m), 7.2-7.5 (5H, m), 7.86 (1H, dd, J=8.0, 1.4 Hz), 7.97 (1H, dd, J=8.0, 1.4 Hz)<br>Mass: 380 (M <sup>+</sup> +H)  |
| (31) | H               | H               | H               | Me              | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.50 (3H, s), 2.3-2.7 (8H, m), 3.1-3.3 (2H, m), 6.28 (1H, br.s), 7.29 (1H, t, J=8.0 Hz), 7.5-7.8 (5H, m), 7.88 (1H, d, J=8 Hz)<br>Mass: 428 (M <sup>+</sup> +H)   |
| (32) | H               | H               | H               | Me              | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.50 (3H, s), 2.4-2.8 (8H, m), 3.0-3.2 (2H, m), 6.15 (1H, m), 7.2-7.6 (5H, m), 7.60 (1H, dd, J=7.6, 1.4 Hz), 7.88 (1H, dd, J=7.6, 1.4 Hz)<br>Mass: 394 (M <sup>+</sup> +H)  |
| (33) | H               | H               | H               | Me              | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.40 (3H, s), 2.59 (3H, s), 2.4-2.8 (8H, m), 3.0-3.2 (2H, m), 6.06 (1H, m), 7.11 (2H, d, J=8 Hz), 7.24 (2H, d, J=8 Hz), 7.30 (1H, t, J=8 Hz), 7.61 (1H, dd, J=7.6, 1.4 Hz), 7.89 (1H, dd, J=7.6, 1.4 Hz)<br>Mass: 374 (M <sup>+</sup> +H) |
| (34) | H               | H               | H               | Me              | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.59 (3H, s), 2.4-2.8 (8H, m), 3.0-3.2 (2H, m), 3.74 (3H, s), 5.99 (1H, m), 6.87 (2H, d, J=8 Hz), 7.25 (2H, d, J=8 Hz), 7.25 (1H, t, J=8 Hz), 7.60 (1H, dd, J=7.6, 1.4 Hz), 7.89 (1H, dd, J=7.6, 1.4 Hz)<br>Mass: 389 (M <sup>+</sup> +H) |
| (35) | H               | H               | H               | Me              | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.59 (3H, s), 2.4-2.8 (8H, m), 3.0-3.2 (2H, m), 6.05 (1H, m), 7.0-7.5 (5H,m), 7.80 (1H, dd, J=7.6, 1.4 Hz), 7.95 (1H, dd, J=7.6, 1.4 Hz)<br>Mass: 378 (M <sup>+</sup> +H)   |

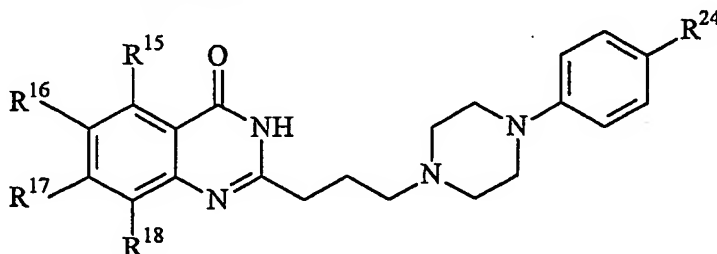
| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |   |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|---|
| (36) | H               | H               | H               | OMe             | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.4-2.8 (8H, m), 3.0-3.2 (2H, m), 3.89 (3H, m), 6.11 (1H, m), 7.1-7.7 (7H, m)<br>Mass: 376 (M <sup>+</sup> +H)   |
| (37) | H               | H               | H               | OMe             | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.6-2.9 (8H, m), 3.0-3.2 (2H, m), 3.88 (3H, m), 6.29 (1H, m), 7.2-7.8 (7H, m)<br>Mass: 444 (M <sup>+</sup> +H)   |
| (38) | H               | H               | H               | OMe             | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.4-2.8 (8H, m), 3.0-3.2 (2H, m), 3.88 (3H, m), 6.15 (1H, m), 7.2-7.7 (7H, m)<br>Mass: 410 (M <sup>+</sup> +H)   |
| (39) | H               | H               | H               | OMe             | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.27 (3H, s), 2.4-2.8 (8H, m), 3.0-3.2 (2H, m), 3.88 (3H, m), 6.07 (1H, m), 7.1-7.7 (7H, m)<br>Mass: 390 (M <sup>+</sup> +H)   |
| (40) | H               | H               | H               | OMe             | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.27 (3H, s), 2.4-2.8 (8H, m), 3.0-3.2 (2H, m), 3.88 (3H, m), 4.09 (3H, s), 5.99 (1H, m), 6.8-7.7 (7H, m)<br>Mass: 406 (M <sup>+</sup> +H)   |
| (41) | H               | H               | H               | Cl              | CN              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): d/ppm 1.98 (2H, quint., J=6.9 Hz), 2.3-2.8 (8H, m), 3.11 (2H, d, J=2.9 Hz), 6.29 (1H, br s), 7.36 (1H, t, J=7.9 Hz), 7.53 (2H, d, J=8.5 Hz), 7.77 (2H, d, J=8.4 Hz), 7.90 (1H, d, J=7.8 Hz), 7.97 (1H, d, J=7.9 Hz), 12.49 (1H, br)<br>Mass (APCI): 405.00 (M <sup>+</sup> +H)  |
| (42) | H               | H               | H               | Cl              | Ac              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): d/ppm 1.99 (2H, quint., J=6.9 Hz), 2.3-2.8 (8H, m), 3.11 (2H, d, J=2.8 Hz), 6.26 (1H, br s), 7.37 (1H, t, J=7.8 Hz), 7.49 (2H, d, J=8.4 Hz), 7.90 (2H, d, J=8.4 Hz), 7.91 (1H, d, J=7.8 Hz), 7.98 (1H, d, J=7.9 Hz), 12.44 (1H, br)<br>Mass (API-ES): 422.2 (M <sup>+</sup> +H) |

Example 14

The following compounds are prepared in a similar manner to that of Example 9.

If necessary, the starting compounds of them were prepared in similar manners of

5 Preparation 17 and Preparation 20.





| No. | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |  |
|-----|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (1) | H               | H               | H               | H               | H               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=6.0 Hz), 2.62 (2H, t, J=5.8 Hz), 2.78 (4H, t, J=5.0 Hz), 2.8-3.0 (2H, m), 3.45 (4H, t, J=5.0 Hz), 6.87 (1H, t, J=7.2 Hz), 6.98 (2H, d, J=7.8 Hz), 7.28 (2H, t, J=8.0 Hz), 7.42 (1H, t, J=7.4 Hz), 7.6-7.8 (2H, m), 8.23 (1H, d, J=8.0 Hz), 12.92 (1H, br s)<br>Mass (APCI): 349.20 (M <sup>+</sup> +H) |
| (2) | H               | H               | H               | Cl              | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.3-2.8 (8H, m), 3.0-3.2 (2H, m), 6.7-7.2 (5H, m), 7.33 (1H, t, J=8.0 Hz), 7.85 (1H, dd, J=8.0, 1.4 Hz), 8.01 (1H, dd, J=8.0, 1.4 Hz)<br>Mass: 383 (M <sup>+</sup> +H)  |
| (3) | H               | H               | H               | Cl              | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.3-3.0 (12H, m), 3.67 (3H, s), 6.8-7.0 (4H, m), 7.36 (1H, t, J=8.0 Hz), 7.88 (1H, dd, J=8.0, 1.4 Hz), 7.99 (1H, dd, J=8.0, 1.4 Hz)<br>Mass: 413 (M <sup>+</sup> +H)  |
| (4) | H               | H               | H               | Cl              | CN              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.3-2.9 (8H, m), 3.1-3.3 (4H, m), 6.97 (2H, d, J=8.0 Hz), 7.06 (1H, t, J=8.0 Hz), 7.55 (2H, d, J=8.0 Hz), 8.00 (1H, dd, J=8.0, 1.2 Hz), 8.02 (1H, dd, J=8.0, 1.2 Hz)<br>Mass: 408 (M <sup>+</sup> +H)   |
| (5) | H               | H               | H               | Cl              | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.18 (3H, s), 2.1-2.9 (8H, m), 2.8-3.0 (4H, m), 6.75 (2H, d, J=8.0 Hz), 7.00 (2H, d, J=8.0 Hz), 7.40 (1H, t, J=8.0 Hz), 7.91 (1H, dd, J=8.0, 1.2 Hz), 8.01 (1H, dd, J=8.0, 1.2 Hz)<br>Mass: 398 (M <sup>+</sup> +H)   |
| (6) | H               | H               | H               | Cl              | Ph              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.3-3.2 (12H, m), 6.9-7.7 (10H, m), 7.80 (1H, dd, J=8.0, 1.2 Hz), 7.95 (1H, dd, J=8.0, 1.2 Hz)<br>Mass: 459 (M <sup>+</sup> +H)   |
| (7) | H               | H               | H               | Cl              | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.3-3.2 (12H, m), 6.7-7.1 (4H, m), 7.35 (1H, t, J=8.0 Hz), 7.86 (1H, dd, J=8.0, 1.2 Hz), 8.00 (1H, dd, J=8.0, 1.2 Hz)<br>Mass: 401 (M <sup>+</sup> +H)  |
| (8) | H               | H               | H               | Cl              | NO <sub>2</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.3-3.0 (12H, m), 6.99 (2H, d, J=9.6 Hz), 7.39 (1H, t, J=7.9 Hz), 7.90 (1H, dd, J=7.9, 1.6 Hz), 8.0-8.2 (3H, m)<br>Mass: 428 (M <sup>+</sup> +H)  |
| (9) | H               | H               | H               | Cl              | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.3-3.0 (8H, m), 3.0-3.2 (4H, m), 7.00 (2H, d, J=8.6 Hz), 7.3-7.6 (3H, m), 7.91 (1H, dd, J=7.9, 1.4 Hz), 8.02 (1H, dd, J=7.9, 1.4 Hz)<br>Mass: 451 (M <sup>+</sup> +H)  |

| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |  |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (10) | H               | H               | H               | Me              | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.52 (3H, s), 2.8-3.0 (2H, m), 6.8-7.1 (4H, m), 7.31 (1H, t, J=8 Hz), 7.62 (1H, d, J=8 Hz), 7.90 (1H, d, J=8 Hz)<br>Mass: 381 (M <sup>+</sup> +H)                            |
| (11) | H               | H               | H               | Me              | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.52 (3H, s), 2.8-3.0 (2H, m), 6.90 (2H, d, J=8 Hz), 7.22 (2H, d, J=8 Hz), 7.28 (1H, t, J=8 Hz), 7.59 (1H, d, J=8 Hz), 7.88 (1H, d, J=8 Hz)<br>Mass: 397 (M <sup>+</sup> +H) |
| (12) | H               | H               | H               | OMe             | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.6-2.0 (4H, m), 2.2-2.8 (5H, m), 3.0-3.3 (4H, m), 3.88 (3H, s), 6.8-7.7 (7H, m)<br>Mass: 413 (M <sup>+</sup> +H)  |
| (13) | H               | H               | H               | OMe             | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.6-2.0 (4H, m), 2.2-2.8 (5H, m), 3.0-3.3 (4H, m), 3.88 (3H, s), 6.8-7.7 (7H, m)<br>Mass: 397 (M <sup>+</sup> +H)  |
| (14) | H               | H               | H               | OMe             | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-3.0 (8H, m), 3.0-3.2 (2H, m), 6.8-7.0 (2H, m), 7.1-7.3 (2H, m), 7.4-7.8 (3H, m)<br>Mass: 401 (M <sup>+</sup> +H)  |
| (15) | H               | Cl              | H               | H               | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.9-3.1 (2H, m), 6.88 (2H, d, J=8 Hz), 7.18 (2H, d, J=8 Hz), 7.55 (1H, d, J=8 Hz), 7.81 (1H, d, J=8 Hz), 7.99 (1H, s)<br>Mass: 417 (M <sup>+</sup> +H)                       |
| (16) | H               | Cl              | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.9-3.1 (2H, m), 6.7-7.1 (4H, m), 7.59 (1H, d, J=8 Hz), 7.79 (1H, d, J=8 Hz), 8.52 (1H, s)<br>Mass: 401 (M <sup>+</sup> +H)  |
| (17) | H               | Cl              | H               | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 2.9-3.1 (2H, m), 6.7-7.2 (5H, m), 7.61 (1H, d, J=8 Hz), 7.80 (1H, d, J=8 Hz), 8.32 (1H, s)<br>Mass: 383 (M <sup>+</sup> +H)  |
| (18) | H               | Cl              | H               | H               | NO <sub>2</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-3.2 (10H, m), 6.8-7.1 (2H, m), 7.62 (1H, d, J=8 Hz), 7.80 (1H, d, J=8 Hz), 7.9-8.1 (3H, m)<br>Mass: 428 (M <sup>+</sup> +H)   |
| (19) | H               | Cl              | H               | H               | Ph              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.0 (2H, m), 2.2-3.2 (10H, m), 6.8-7.8 (10H, m), 7.81 (1H, d, J=8 Hz), 7.98 (1H, s)<br>Mass: 459 (M <sup>+</sup> +H)   |

| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |  |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|--|
| (20) | Cl              | H               | H               | H               | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 2.9-3.2 (4H, m), 6.89 (2H, d, J=8 Hz), 7.26 (2H, d, J=8 Hz), 7.3-7.7 (3H, m)<br>Mass: 417 (M <sup>+</sup> +H)  |
| (21) | H               | H               | H               | H               | Br              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.1-3.3 (4H, m), 6.84 (2H, d, J=9.2 Hz), 7.32 (2H, d, J=9.2 Hz), 7.37 (1H, t, J=9.0 Hz), 7.71 (1H, d, J=9.0 Hz), 7.78 (1H, td, J=9.0, 1.2 Hz), 8.04 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 428 (M <sup>+</sup> +H) |
| (22) | H               | H               | H               | H               | Cl              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.1-3.3 (4H, m), 6.88 (2H, d, J=9.2 Hz), 7.35 (2H, d, J=9.2 Hz), 7.38 (1H, t, J=9.0 Hz), 7.71 (1H, d, J=9.0 Hz), 7.78 (1H, td, J=9.0, 1.2 Hz), 8.05 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 383 (M <sup>+</sup> +H) |
| (23) | H               | H               | H               | H               | F               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.1-3.3 (4H, m), 6.8-7.0 (4H, m), 7.40 (1H, t, J=9.0 Hz), 7.79 (1H, d, J=9.0 Hz), 7.82 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 367 (M <sup>+</sup> +H)                                |
| (24) | H               | H               | H               | H               | OMe             | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 2.8-3.0 (4H, m), 3.67 (3H, m), 6.6-7.0 (4H, m), 7.40 (1H, t, J=9.0 Hz), 7.56 (1H, d, J=9.0 Hz), 7.70 (1H, td, J=9.0, 1.2 Hz), 8.05 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 379 (M <sup>+</sup> +H)                  |
| (25) | H               | H               | H               | H               | OH              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 2.8-3.0 (4H, m), 6.6-7.0 (4H, m), 7.43 (1H, t, J=9.0 Hz), 7.58 (1H, d, J=9.0 Hz), 7.76 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 365 (M <sup>+</sup> +H)                                |
| (26) | H               | H               | H               | H               | NO <sub>2</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.2-3.5 (4H, m), 7.02 (2H, d, J=8.0 Hz), 7.33 (1H, t, J=9.0Hz), 7.52 (1H, d, J=9.0Hz), 7.69 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz), 8.07 (2H, d, J=8.0 Hz)<br>Mass: 394 (M <sup>+</sup> +H)   |
| (27) | H               | H               | H               | H               | NH <sub>2</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 2.8-3.0 (4H, m), 6.44 (2H, d, J=8.0 Hz), 6.81 (2H, d, J=8 Hz), 7.39 (1H, t, J=9.0 Hz), 7.57 (1H, d, J=9.0 Hz), 7.75 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 364 (M <sup>+</sup> +H)   |

| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup>    |  |
|------|-----------------|-----------------|-----------------|-----------------|--------------------|--|
| (28) | H               | H               | H               | H               | N(Me) <sub>2</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 2.8-3.0 (4H, m), 6.5-7.0 (4H, m), 7.39 (1H, t, J=9.0 Hz), 7.57 (1H, d, J=9.0 Hz), 7.75 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 392 (M <sup>+</sup> +H)  |
| (29) | H               | H               | H               | H               | NHBz               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.0-3.2 (4H, m), 6.7-8.2 (14H, m)<br>Mass: 467 (M <sup>+</sup> +H)   |
| (30) | H               | H               | H               | H               | NHAc               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 1.98 (3H, s), 2.3-2.7 (8H, m), 2.8-3.0 (4H, m), 6.81 (2H, d, J=8 Hz), 7.38 (2H, d, J=8 Hz), 7.39 (1H, t, J=9.0 Hz), 7.57 (1H, d, J=9.0 Hz), 7.77 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 406 (M <sup>+</sup> +H) |
| (31) | H               | H               | H               | H               | CN                 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.3-3.5 (4H, m), 6.98 (2H, d, J=8 Hz), 7.39 (1H, t, J=9.0 Hz), 7.56 (2H, d, J=8 Hz), 7.57 (1H, d, J=9.0 Hz), 7.80 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 374 (M <sup>+</sup> +H)               |
| (32) | H               | H               | H               | H               | COOH               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.3-3.5 (4H, m), 6.90 (2H, d, J=8 Hz), 7.35 (1H, t, J=9.0 Hz), 7.57 (1H, d, J=9.0 Hz), 7.71 (2H, d, J=8 Hz), 7.80 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 393 (M <sup>+</sup> +H)               |
| (33) | H               | H               | H               | H               | OPh                | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.0-3.3 (4H, m), 6.8-7.0 (7H, m), 7.2-7.5 (3H, m), 7.60 (1H, d, J=8 Hz), 7.59 (1H, t, J=8 Hz), 8.06 (1H, d, J=8.0 Hz)<br>Mass: 441 (M <sup>+</sup> +H)   |
| (34) | H               | H               | H               | H               | Ac                 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.3-3.5 (4H, m), 6.93 (2H, d, J=8Hz), 7.42 (1H, t, J=9.0 Hz), 7.58 (1H, d, J=9.0 Hz), 7.77 (2H, d, J=8 Hz), 7.80 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 391 (M <sup>+</sup> +H)                |
| (35) | H               | H               | H               | H               | Ph                 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.3-3.5 (4H, m), 6.9-8.1 (13H, m)<br>Mass: 391 (M <sup>+</sup> +H)   |

| No.  | R <sup>15</sup> | R <sup>16</sup> | R <sup>17</sup> | R <sup>18</sup> | R <sup>24</sup> |   |
|------|-----------------|-----------------|-----------------|-----------------|-----------------|---|
| (36) | H               | H               | H               | H               | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.1 (3H, s), 2.3-2.7 (8H, m), 3.3-3.5 (4H, m), 6.88 (2H, d, J=8.0 Hz), 6.81 (2H, d, J=8 Hz), 7.39 (1H, t, J=9.0 Hz), 7.57 (1H, d, J=9.0 Hz), 7.75 (1H, td, J=9.0, 1.2 Hz), 8.06 (1H, dd, J=9.0, 1.2 Hz)<br>Mass: 363 (M <sup>+</sup> +H) |
| (37) | H               | H               | H               | H               | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.3-3.5 (4H, m), 6.8-8.2 (8H, m)<br>Mass: 417 (M <sup>+</sup> +H)   |

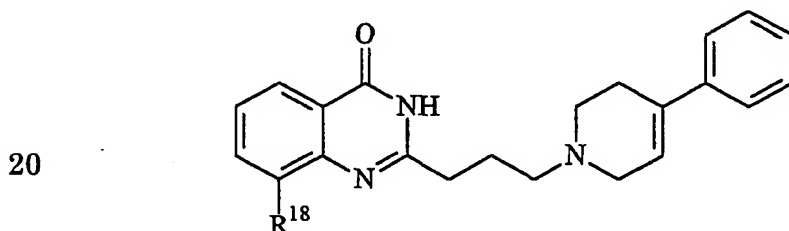
**Example 15**

A mixture of 8-chloro-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone (50 mg), 1-methylpiperazine (19.8 mg), palladium (II) acetate (2.96 mg), 2-(di-*t*-butylphosphino)biphenyl (7.86 mg), sodium *t*-butoxide (23 mg) in toluene (0.4 ml) and tetrahydrofuran (0.2 ml) was stirred at 80 °C under nitrogen atmosphere overnight. The mixture was cooled, diluted with water and extracted with dichloromethane twice. The combined extracts were dried over magnesium sulfate and concentrated. The residue was purified by preparative thin layer chromatography on silica gel using 10% methanol in dichloromethane to give the 8-(4-methyl-1-piperazinyl)-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone.

Mass (APCI): 444.3 (M<sup>+</sup>+H)

**Example 16**

The following compounds are prepared in a similar manner to that of **Example 15**.



| No. | R <sup>18</sup>                    |   |
|-----|------------------------------------|---|
| (1) | 1-piperidyl                        | Mass (ESI): 429.3 (M <sup>+</sup> +H)   |
| (2) | (2R,6S)-2,6-Dimethyl-4-morpholinyl | Mass (ESI): 459.3 (M <sup>+</sup> +H)   |
| (3) | 1-pyrrolidinyl                     | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.1 (2H,m), 2.3-2.8 (8H,m), 3.05 (2H, br.s), 6.20 (1H, m), 7.0-7.9 (8H, m)<br>Mass: 415 (M <sup>+</sup> +H) |

| No. | R <sup>18</sup> |   |
|-----|-----------------|---|
| (4) | 4-morpholinyl   | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.8-2.1 (2H,m), 2.1-3.2 (16H, m), 3.7-3.9 (2H, m), 6.10 (1H, m), 7.0-8.0 (8H, m)<br>Mass: 431 (M <sup>+</sup> +H) |

Example 17

To a suspension of  
 8-nitro-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone (50 mg)  
 5 in ethanol (10 ml) and water (5 ml) were added iron powder (57 mg) and ammonium chloride (5.8 mg). After stirring under reflux for 1 hour, the mixture was filtered and the filtrate was concentrated. The residue was purified by preparative thin layer chromatography using 10% methanol in dichloromethane as an eluent to give  
 8-Amino-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone as a  
 10 brown powder.  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 1.80 - 2.20 (2H, m), 2.30 - 3.30 (10H, m), 5.58 (2H, brs), 6.13 (1H, s), 6.80 - 7.70 (8H, m), 12.03 (1H, brs)  
 Mass (ESI): 361.4 (M<sup>+</sup>+H)

15 Example 18

A slurry of  
 8-amino-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone (40 mg),  
 37% aqueous formaldehyde (0.088 ml), acetic acid (0.032 ml) and sodium  
 cyanoborohydride (70 mg) in acetonitrile (10 ml) was stirred at room temperature overnight.  
 20 The reaction was quenched with aqueous sodium hydrogen carbonate and extracted with dichloromethane three times. The combined extracts were dried over magnesium sulfate and concentrated. The residue was purified by preparative thin layer chromatography using 10% methanol in dichloromethane as an eluent to give  
 8-dimethylamino-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinon  
 25 e (18 mg) as a yellow solid.  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 1.80 - 2.20 (2H, m), 2.30 - 2.90 (10H, m), 2.96 (6H, s), 6.15 (1H, s), 7.00 - 7.70 (8H, m), 12.15 (1H, brs)  
 Mass (ESI): 389.4 (M<sup>+</sup>+H)

30 Example 19

The following compounds are prepared in a similar manner to that of Preparation 18.

- (1) 8-benzylamino-2-{3-[4-phenyl-3,6-dihydro-1(2H)-pyridinyl]propyl}-

## 4(3H)-quinazolinone

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.1 (2H, m), 2.1-3.0 (8H, m), 3.0-3.2 (2H, m), 4.47 (2H, d, J = 6Hz), 6.09 (1H, m), 6.56 (1H, t, J = 6.2Hz), 6.69 (1H, d, J = 6.2Hz), 7.0-7.5 (12H, m)

5 Mass: 451 (M<sup>+</sup>+H)

Example 20

A solution of

8-amino-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone (30 mg)  
10 and acetic anhydride (17 mg) in dichloromethane was stirred at room temperature overnight. The mixture was concentrated and purified by preparative thin layer chromatography (10% methanol in dichloromethane) to give N-{4-Oxo-2-[(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-3,4-dihydro-8-quinazolinyl}acetamide as a pale yellow powder.

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.80 - 2.20 (2H, m), 2.22 (3H, s), 2.30 - 3.00 (8H, m),  
15 3.10 (2H, d, J=3.0 Hz), 6.10 (1H, s), 7.10 - 7.60 (6H, m), 7.70 (1H, dd, J=1.4, 8.0 Hz), 8.57 (1H, dd, J=1.4, 8.0 Hz), 9.51 (1H, s), 12.38 (1H, brs).

Mass (ESI): 403.4 (M<sup>+</sup>+H)

Example 21

20 A mixture of

8-iodo-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone (45 mg), (trimethylsilyl)acetylene (14.1 mg), dichlorobis(triphenylphosphine)palladium (II) (6.7 mg), copper iodide (1.82 mg) and triethylamine (0.027 ml) in N,N-dimethylformamide was stirred at room temperature under nitrogen overnight. The mixture was diluted with water  
25 and extracted with dichloromethane twice. The combined extracts were washed with water twice, dried over magnesium sulfate and concentrated. The residue was purified by preparative thin layer chromatography using 10% methanol in dichloromethane as an eluent to give 2-[3-(4-Phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-8-[(trimethylsilyl)ethynyl]-4(3H)-quinazolinone as a colorless powder (13 mg).

30 <sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 0.33 (9H, s), 0.70 - 3.30 (12H, m), 6.08 (1H, s), 7.10 - 8.30 (8H, m)

Mass (ESI): 441.64 (M<sup>+</sup>+H)

Example 22

35 A solution of 2-[3-(4-Phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-8-[(trimethylsilyl)ethynyl]-4(3H)-quinazolinone (202 mg) in methanol was stirred at room

temperature in the presence of potassium carbonate (190 mg) for 3 hours. The mixture was diluted with water and extracted with dichloromethane twice. The combined extracts were dried over magnesium sulfate and concentrated. The residue was purified by

5 dichloromethane as an eluent to give

8-Ethynyl-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone the objective compound, which was converted to the corresponding hydrochloride salt (59 mg) by treatment of 4N hydrogen chloride in ethyl acetate.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, d): 2.10 - 2.40 (2H, m), 2.60 - 3.00 (4H, m), 3.00 - 4.20 (6H, m),  
10 4.51 (1H, s), 6.22 (1H, s), 7.10 - 7.80 (6H, m), 7.94 (1H, dd, J=1.5, 7.9 Hz), 8.11  
(1H, dd, J=1.5, 7.9 Hz), 10.32 (1H, brs), 12.44 (1H, brs)

Mass (APCI): 370.07 (M<sup>+</sup>+H)

#### Example 23

15 The following compounds are prepared in a similar manner to that of Example 21.

(1) 8-phenyl-2-{3-[4-phenyl-3,6-dihydro-1(2H)-pyridinyl]propyl}-  
4(3H)-quinazolinone

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.1 (2H, m), 2.1-3.0 (8H, m), 3.0-3.2 (2H, m), 6.09 (1H, m), 7.0-8.2 (13H, m)

20 Mass: 422 (M<sup>+</sup>+H)

#### Example 24

Under a nitrogen atmosphere, (diethylamino)sulfur trifluoride (0.363 mL, 2.75 mmol) was added dropwise to a solution of

25 2-[3-(4-hydroxy-4-phenyl-1-piperidyl)propyl]-4(3H)-quinazolinone (100 mg, 0.275 mmol) in dichloromethane (10mL) at -78 °C. The mixture was stirred for 2 hours (to -50 °C). (Diethylamino)sulfur trifluoride (0.363mL, 2.75mmol) was added, and the mixture was stirred for further 2h (to 0 °C). Quenched with saturated aqueous sodium hydrogencarbonate, the organic materials were extracted with ethyl acetate. Purification

30 over silica gel chromatography gave

2-[3-(4-fluoro-4-phenyl-1-piperidyl)propyl]-4(3H)-quinazolinone (34mg, 33.8%).

<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 1.9-2.1 (4H, m), 2.5-2.9 (6H, m), 2.9-3.1 (4H, m), 7.31 (1H, t, J=7.1 Hz), 7.44 (3H, t, J=7.9 Hz), 7.6-7.8 (4H, m), 8.29 (1H, d, J=7.9 Hz).

MS (APCI): 365.80 (M<sup>+</sup>+H)

35

#### Example 25



2-{3-[4-phenyl-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone (110 mg, 0.310 mmol) was suspended in a mixed solvent of chloroform (1 mL) and ethyl acetate (2 mL). To this suspension, a solution of hydrogen chloride (4M, 2.33 mL) was added, and the mixture was stirred for 1 hour. The white precipitate was collected by filtration to  
 5 give 2-{3-[4-phenyl-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone hydrochloride (124 mg, 104 %) as product.

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.29 (2H, quint., J=7.6 Hz), 2.8-2.9 (4H, m), 3.30 (2H, dd, J=8.6, 6.8 Hz), 3.5-4.2 (4H, m), 6.21 (1H, br s), 7.2-7.6 (6H, m), 7.73 (1H, d, J=7.7 Hz), 7.86 (1H, t, J=6.9 Hz), 8.13 (1H, d, J=7.9 Hz).

10 MS (APCI): 346.13 (M<sup>+</sup>+H)

### Example 26

The following compounds are prepared in a similar manner to that of Preparation 25.

- 15 (1) 8-chloro-2-{3-[4-(4-acetylphenyl)-3,6-dihydropyridin-1(2H)-yl]propyl}-4(3H)-quinazolinone hydrochloride  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.1-2.4 (2H, m), 2.59 (3H, s), 2.7-3.0 (4H, m), 3.2-3.5 (3H, m), 3.6-4.2 (3H, m), 6.40 (1H, br s), 7.46 (1H, t, J=7.8 Hz), 7.65 (2H, d, J=8.4 Hz), 7.9-8.0 (3H, m), 8.06 (1H, d, J=7.9 Hz), 10.65 (1H, br), 12.54 (1H, br)  
 20 Mass (APCI): 422.07 (M<sup>+</sup>+H)
- (2) 8-chloro-2-{3-[4-phenyl-3,6-dihydropyridin-1(2H)-yl]propyl}-4(3H)-quinazolinone hydrochloride  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.1-2.45 (2H, m), 2.65-3.05 (4H, m), 3.15-3.45 (3H, m), 3.55-3.9 (2H, m), 3.95-4.15 (1H, m), 6.20 (1H, s), 7.3-7.55 (6H, m), 7.95 (1H, dd, J=7.8, 1.4 Hz), 8.05 (1H, dd, J=7.8, 1.4 Hz)  
 25 (3) 8-chloro-2-{3-[4-[4-(trifluoromethyl)phenyl]-3,6-dihydropyridin-1(2H)-yl]propyl}-4(3H)-quinazolinone hydrochloride  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 2.15-2.35 (2H, m), 2.75-2.95 (4H, m), 3.25-3.45 (2H, m), 3.45-4.20 (4H, m), 6.37 (1H, s), 7.45 (1H, t, J=7.8 Hz), 7.73 (4H, s), 7.94 (1H, dd, J=7.8, 1.4 Hz), 8.05 (1H, dd, J=7.8, 1.4 Hz), 10.59 (1H, br s), 12.53 (1H, br s)  
 30 (4) 8-Chloro-2-{3-[4-(4-(hydroxymethyl)phenyl)-3,6-dihydropyridin-1(2H)-yl]propyl}4(3H)-quinazolinone hydrochloride  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 2.15-2.40 (2H, m), 2.7-2.9 (4H, m), 3.6-4.2 (6H, m), 4.50 (2H, s), 5.72 (1H, s), 6.18 (1H, s), 7.32 (2H, d, J=8.3 Hz), 7.4-7.5 (3H, m), 7.94 (1H, dd, J=7.8, 1.4 Hz), 8.06 (1H, dd, J=7.8, 1.4 Hz), 10.59 (1H, br s), 12.53 (1H, br s)  
 35

br s)

#### Example 27

Under a nitrogen atmosphere, 1M boron tribromide in dichloromethane (1.99 ml)  
5 was added to a solution of  
2-{3-[4-(4-methoxyphenyl)piperidin-1-yl]propyl}-4(3H)-quinazolinone (150 mg) in  
dichloromethane (7.5 ml) at 0 °C. The mixture was stirred for 2 hours and the solvent was  
evaporated. The residue was diluted with aqueous sodium hydrogencarbonate and the  
aqueous phase was removed with decant. The crude product was triturated with a mixture  
10 of chloroform and methanol (10:1) and the resulting precipitate was collected by filtration.  
The precipitate was washed with chloroform-methanol and dried under reduced pressure to  
afford 2-{3-[4-(4-hydroxyphenyl)piperidin-1-yl]propyl}-4(3H)-quinazolinone (122 mg).  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.7-2.1 (4H, m), 2.1-2.3 (2H, m), 2.6-3.3 (9H, m), 6.72  
(2H, d, J=8.5 Hz), 6.90 (2H, d, J=8.5 Hz), 7.51 (1H, dt, J=8.1, 1.1 Hz), 7.63 (1H, d,  
15 J=8.0 Hz), 7.82 (1H, dt, J=8.4, 1.5 Hz), 8.11 (1H, dd, J=7.9, 1.1 Hz)  
Mass: 361.80(M<sup>+</sup>)

#### Example 28

The following compounds are prepared in a similar manner to that of Example 27.  
20 (1) 2-{3-[4-(4-hydroxyphenyl)-3,6-dihydropyridin-1(2H)-yl]propyl}-  
4(3H)-quinazolinone  
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 2.1-2.4 (2H, m), 2.65-2.95 (4H, m), 3.2-3.5 (3H, m),  
3.6-4.2 (3H, m), 6.03 (1H, s), 6.77 (2H, d, J=8.7 Hz), 7.32 (2H, d, J=8.7 Hz), 7.56  
(1H, t, J=7.3 Hz), 7.67 (1H, d, J=8.1 Hz), 7.85 (1H, t, J=7.4 Hz), 8.14 (1H, dd,  
25 J=7.8, 1.2 Hz)  
Mass: 362.3 (M<sup>+</sup>+H)

#### Example 29

Under a nitrogen atmosphere, dimethylsulfoxide (0.093 ml) in dichloromethane  
30 was added to a stirred solution of oxalylchloride (0.06 ml) in dichloromethane (10 ml) at  
-78 °C. The mixture was stirred for 1 hour. To this solution was added a solution of  
2-{3-[4-(4-hydroxymethyl)phenyl]-3,6-dihydropyridin-1(2H)-yl}propyl}-  
4(3H)-quinazolinone (130 mg) in a mixture of dichloromethane (1.5 ml) and  
dimethylsulfoxide (0.5 ml) at -70 °C. The mixture was stirred for 30 minutes and to this  
35 solution was added triethyl amine (0.25 ml) at the same temperature. The whole mixture  
was gradually warmed to -20 °C and the reaction was quenched with water. The

aqueous layer was separated and the organic layer was washed with brine, dried over magnesium sulfate. After evaporation of the solvent, the residue was purified by preparative TLC eluting with chloroform-methanol to afford

2-{3-[4-(4-formylphenyl)-3,6-dihydropyridin-1(2H)-yl]propyl}-4(3H)-quinazolinone

5 (47mg).

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.85-2.1 (2H, m), 2.4-2.8 (10H, m), 3.12 (2H, d, J=2.8 Hz), 6.35 (1H, s), 7.42 (1H, t, J=6.9 Hz), 7.5-7.65 (3H, m), 7.7-7.8 (1H, m), 7.86 (2H, d, J=8.3 Hz), 8.04 (1H, dd, J=7.9, 1.3 Hz), 9.97 (1H, s), 12.21 (1H, br s)

Mass: 374.0 (M<sup>+</sup>)

10

### Example 30

3-Chloro-2-({4-[4-(4-cyanophenyl)-3,6-dihydro-1(2H)-pyridinyl]butanoyl}amino) benzamide (152 mg, 0.359 mmol) was dissolved in a mixed solvent of dioxane (2 mL) and methanol (3 mL). An aqueous solution of sodium hydroxide (1 M, 1.08 mL) was added to

15 the solution at room temperature, and the mixture was stirred at that temperature for 1 hour.

The organic materials were extracted with chloroform, and the organic layer was washed with water and dried over sodium sulfate. The crude product was suspended in a mixed solvent of chloroform (1mL) and ethyl acetate (2mL). To this suspension, a solution of hydrogen chloride (4M, 2.0mL) was added, and the mixture was stirred for 1 hour. The

20 white precipitate was collected by filtration to give 8-chloro-2-{3-[4-(4-cyanophenyl)-3,6-dihydropyridin-1(2H)-yl]propyl}-4(3H)-quinazolinone (140mg, 88.3%) as product.

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.1-2.3 (2H, m), 2.7-2.9 (4H, m), 3.2-3.4 (3H, m), 3.7-4.0 (2H, m), 4.0-4.2 (1H, m), 6.44 (1H, br s), 7.46 (1H, t, J=7.9 Hz), 7.70 (2H, d, J=8.5 Hz), 7.87 (2H, d, J=8.4 Hz), 7.95 (1H, d, J=7.8 Hz), 8.06 (1H, d, J=7.9

25 Hz), 10.51 (1H, br), 12.53 (1H, br)

Mass (APCI): 405.07 (M<sup>+</sup>+H)

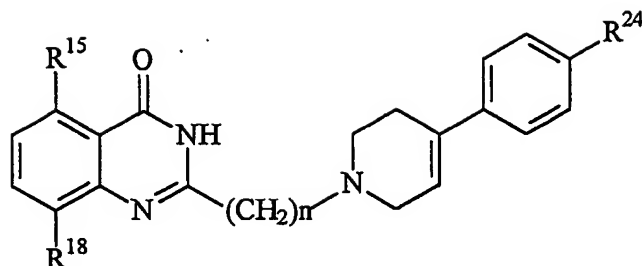
### Example 31

The following compounds are prepared in a similar manner to that of Example 9.

30 If necessary, the starting compounds of them were prepared in similar manners of Preparation 17 and Preparation 20.

35

5



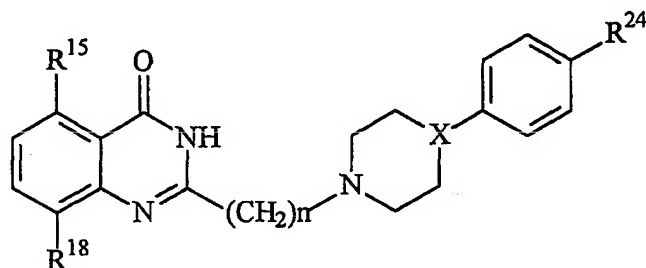
| No. | R <sup>15</sup> | R <sup>18</sup> | R <sup>24</sup> | n |  |
|-----|-----------------|-----------------|-----------------|---|--|
| (1) | Cl              | H               | CN              | 1 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.6-2.8 (2H, m), 2.8-3.0 (2H, m), 3.3-3.5 (2H, m), 3.66 (2H, s), 6.18 (1H, m), 7.3-7.8 (7H, m)<br>Mass: 377 (M <sup>+</sup> +H)  |
| (2) | Cl              | H               | H               | 2 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.7-3.1 (4H, m), 3.2-3.4 (2H, m), 6.39 (1H, m), 7.2-7.9 (8H, m)<br>Mass: 366 (M <sup>+</sup> +H)   |
| (3) | Cl              | H               | CN              | 2 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.7-3.1 (4H, m), 3.2-3.4 (2H, m), 6.39 (1H, m), 7.2-7.8 (7H, m)<br>Mass: 391 (M <sup>+</sup> +H)   |
| (4) | Cl              | H               | OMe             | 2 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.2-2.8 (8H, m), 3.2-3.4 (2H, m), 3.82 (3H, s), 6.03 (1H, m), 6.88 (1H, d J = 8.6Hz), 7.2-7.8 (6H, m)<br>Mass: 396 (M <sup>+</sup> +H)   |
| (5) | H               | Me              | OMe             | 2 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.3-2.5 (2H, m), 2.52 (3H, s), 2.6-2.9 (6H, m), 3.74 (3H, s), 6.04 (1H, m), 6.88 (2H, d, J = 8Hz), 7.2-7.4 (3H, m), 7.62 (1H, d, J = 8Hz), 7.90 (1H, d, J = 8Hz)<br>Mass: 376 (M <sup>+</sup> +H)  |
| (6) | H               | Me              | CN              | 2 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.4-2.5 (2H, m), 2.52 (3H, s), 2.6-2.9 (6H, m), 6.40 (1H, m), 7.31 (1H, t, J = 8Hz), 7.6-7.8 (5H, m), 7.90 (1H, d, J = 8Hz)<br>Mass: 371 (M <sup>+</sup> +H)   |
| (7) | H               | Me              | CF <sub>3</sub> | 2 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.4-2.5 (2H, m), 2.52 (3H, s), 2.6-2.9 (6H, m), 6.35 (1H, m), 7.33 (1H, t, J = 8Hz), 7.6-7.8 (5H, m), 7.91 (1H, d, J = 8Hz)<br>Mass: 414 (M <sup>+</sup> +H)   |
| (8) | H               | H               | H               | 2 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.72 (2H, br), 2.9-3.0 (6H, m), 3.38 (2H, q, J=3.1 Hz), 6.10 (1H, br s), 7.3-7.5 (6H, m), 7.62 (1H, d, J=7.3 Hz), 7.72 (1H, t, J=7.6 Hz), 8.25 (1H, d, J=6.5 Hz).<br>Mass (APCI): 331.67 (M <sup>+</sup> +H)   |
| (9) | H               | H               | H               | 4 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.6-1.9 (2H, m), 1.95 (2H, quint., J=7.3 Hz), 2.5-2.7 (4H, m), 2.7-2.9 (4H, m), 3.22 (2H, q, J=3.1 Hz), 6.06 (1H, br s), 7.2-7.5 (6H, m), 7.67 (1H, d, J=6.8 Hz), 7.75 (1H, t, J=6.7 Hz), 8.26 (1H, d, J=6.6 Hz).<br>Mass (APCI): 360.20 (M <sup>+</sup> +H) |

Example 32

The following compounds are prepared in a similar manner to that of Example 9.  
If necessary, the starting compounds of them were prepared in similar manners of  
Preparation 17, Preparation 20 and preparation 23-(2)

5

10



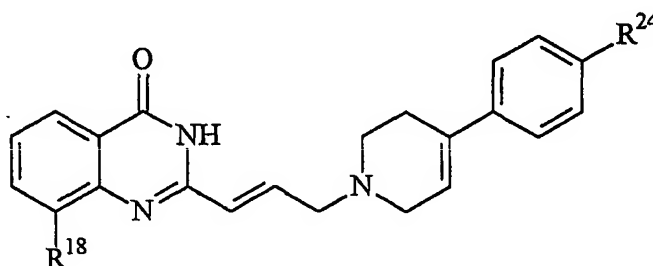
| No. | R <sup>15</sup> | R <sup>18</sup> | R <sup>24</sup> | nX  |  |
|-----|-----------------|-----------------|-----------------|-----|--|
| (1) | H               | Me              | Cl              | 2N  | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.51 (7H, m), 2.6-2.8 (4H, m), 2.8-3.0 (4H, m), 3.1-3.3 (4H, m), 6.92 (2H, d, J = 8Hz), 7.21 (2H, d, J = 8Hz), 7.31 (1H, t, J = 8Hz), 7.61 (1H, d, J = 8Hz), 7.91 (1H, d, J = 8Hz)<br>Mass: 383 (M <sup>+</sup> +H)  |
| (2) | Cl              | H               | Ph              | 2N  | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.6-3.0 (8H, m), 3.1-3.3 (4H, m), 7.0-7.8 (12H, m)<br>Mass: 445(M <sup>+</sup> +H)   |
| (3) | H               | Me              | CN              | 2N  | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.4-2.7 (7H, m), 2.6-2.8 (4H, m), 3.2-3.3 (4H, m), 7.01 (2H, d, J = 8Hz), 7.33 (1H, t, J = 8Hz), 7.56 (2H, d, J = 8Hz), 7.63 (1H, d, J = 8Hz), 7.91 (1H, d, J = 8Hz)<br>Mass: 374 (M <sup>+</sup> +H)  |
| (4) | H               | Cl              | CN              | 2N  | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.5-2.7 (4H, m), 2.7-2.9 (4H, m), 3.1-3.3 (4H, m), 6.93 (2H, d, J = 8Hz), 7.22 (2H, d, J = 8Hz), 7.36 (1H, t, J = 8Hz), 7.87 (1H, d, J = 8Hz), 8.01 (1H, d, J = 8Hz)<br>Mass: 404 (M <sup>+</sup> +H)  |
| (5) | H               | H               | Bzl             | 2CH | <sup>1</sup> H NMR (CDCl <sub>3</sub> , δ): 1.3-1.9 (5H, m), 2.07 (2H, t, J=11.5 Hz), 2.60 (2H, d, J=6.3 Hz), 2.7-2.9 (4H, m), 3.08 (2H, d, J=11.9 Hz), 7.1-7.4 (5H, m), 7.43 (1H, t, J=7.4 Hz), 7.61 (1H, d, J=7.1 Hz), 7.72 (1H, t, J=6.9 Hz), 8.27 (1H, d, J=6.5 Hz).<br>Mass (API-ES): 348.3 (M <sup>+</sup> +H) |
| (6) | H               | H               | Bzl             | 2 N | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.65 (8H, br), 2.8-2.9 (4H, m), 3.57 (2H, s), 7.2-7.4 (5H, m), 7.43 (1H, t, J=7.4 Hz), 7.61 (1H, d, J=7.2 Hz), 7.72 (1H, t, J=7.6 Hz), 8.27 (1H, d, J=7.9 Hz)<br>Mass (API-ES): 349.4 (M <sup>+</sup> +H)  |

Example 33

The following compounds are prepared in a similar manner to that of Example 9.  
If necessary, the starting compounds of them were prepared in similar manners of  
Preparation 17 and Preparation 20.

5

10



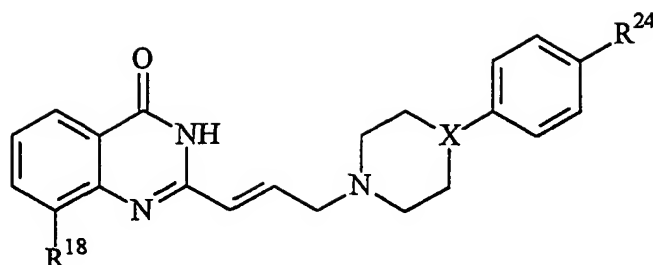
| No. | R <sup>18</sup> | R <sup>24</sup> |  |
|-----|-----------------|-----------------|--|
| (1) | Cl              | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (2H, m), 2.7-2.9 (2H, m), 3.01 (2H, d, J = 3.0Hz), 3.46 (2H, dd, J = 6.0, 1.2Hz), 6.02 (1H, m), 6.30 (1H, d, J = 11.6Hz), 7.0-7.4 (6H, m), 7.81 (1H, dd, J = 8, 1.2Hz), 8.20 (1H, dd, J = 8, 1.2Hz)<br>Mass: 396(M <sup>+</sup> +H)          |
| (2) | Cl              | Cl              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (2H, m), 2.7-2.9 (2H, m), 3.2-3.3 (2H, m), 3.4-3.6 (2H, m), 6.10 (1H, m), 6.55 (1H, d, J = 11.6Hz), 7.0-7.4 (6H, m), 7.81 (1H, dd, J = 8, 1.2Hz), 8.20 (1H, dd, J = 8, 1.2Hz)<br>Mass: 413 (M <sup>+</sup> +H)                               |
| (3) | Cl              | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (2H, m), 2.84 (2H, t, J = 5.6Hz), 3.30 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.10 (1H, m), 6.61 (1H, d, J = 11.6Hz), 7.0-7.4 (6H, m), 7.83 (1H, dd, J = 8, 1.2Hz), 8.19 (1H, dd, J = 8, 1.2Hz)<br>Mass: 445 (M <sup>+</sup> +H)               |
| (4) | Cl              | OMe             | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (2H, m), 2.82 (2H, t, J = 5.4Hz), 3.30 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 3.81 (3H, s), 6.00 (1H, m), 6.84 (1H, d, J = 11.6Hz), 6.8-7.4 (6H, m), 7.80 (1H, dd, J = 8, 1.2Hz), 8.20 (1H, dd, J = 8, 1.2Hz)<br>Mass: 408 (M <sup>+</sup> +H) |
| (5) | Me              | OMe             | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (5H, m), 2.84 (2H, t, J = 5.4Hz), 3.30 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 3.81(3H, s), 6.01 (1H, m), 6.58 (1H, d, J = 11.6Hz), 6.8-7.4 (6H, m), 7.58 (1H, dd, J = 8, 1.2Hz), 8.13 (1H, dd, J = 8, 1.2Hz)<br>Mass: 388(M <sup>+</sup> +H)   |
| (6) | Me              | Me              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.23 (3H, s), 2.5-2.7 (5H, m), 2.84 (2H, t, J = 5.4Hz), 3.30 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.06(1H, m), 6.62 (1H, d, J = 11.6Hz), 7.0-7.4 (6H, m), 7.59 (1H, dd, J = 8, 1.2Hz), 8.10 (1H, dd, J = 8, 1.2Hz)<br>Mass: 372 (M <sup>+</sup> +H)  |

| No.  | R <sup>18</sup> | R <sup>24</sup> |   |
|------|-----------------|-----------------|---|
| (7)  | Me              | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.2-2.4 (8H, m), 2.81 (2H, t, J = 5.4Hz), 3.22 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.20 (1H, m), 6.78 (1H, d, J = 11.6Hz), 7.0-7.6 (7H, m), 8.12 (1H, dd, J = 8, 1.2Hz)<br>Mass: 426 (M <sup>+</sup> +H)           |
| (8)  | Me              | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.2-2.4 (8H, m), 2.81 (2H, t, J = 5.4Hz), 3.22 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.20 (1H, m), 6.78 (1H, d, J = 11.6Hz), 7.0-7.6 (7H, m), 8.12 (1H, dd, J = 8, 1.2Hz)<br>Mass: 376 (M <sup>+</sup> +H)           |
| (9)  | Me              | Cl              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.2-2.4 (8H, m), 2.81 (2H, t, J = 5.4Hz), 3.22 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.23 (1H, m), 6.55 (1H, d, J = 11.6Hz), 7.0-7.6 (7H, m), 8.00 (1H, dd, J = 8, 1.2Hz)<br>Mass: 392 (M <sup>+</sup> +H)           |
| (10) | H               | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.6 (2H, m), 2.86 (2H, t, J = 5.4Hz), 3.34 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.20 (1H, m), 6.59 (1H, d, J = 11.6Hz), 7.0-7.8 (8H, m), 8.26 (1H, d, J = 7.8Hz)<br>Mass: 412 (M <sup>+</sup> +H)               |
| (11) | H               | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.6 (2H, m), 2.86 (2H, t, J = 5.4Hz), 3.32 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.03 (1H, m), 6.59 (1H, d, J = 11.6Hz), 7.0-7.8 (8H, m), 8.32 (1H, d, J = 7.8Hz)<br>Mass: 362 (M <sup>+</sup> +H)               |
| (12) | H               | OMe             | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.6 (2H, m), 2.86 (2H, t, J = 5.4Hz), 3.32 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 3.77 (3H, s), 6.03 (1H, m), 6.59 (1H, d, J = 11.6Hz), 6.8-7.8 (8H, m), 8.29 (1H, d, J = 7.8Hz)<br>Mass: 374 (M <sup>+</sup> +H) |
| (13) | H               | Cl              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.6 (2H, m), 2.86 (2H, t, J = 5.4Hz), 3.32 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.05 (1H, m), 6.51 (1H, d, J = 11.6Hz), 6.8-7.8 (8H, m), 8.22 (1H, d, J = 7.8Hz)<br>Mass: 378 (M <sup>+</sup> +H)               |
| (14) | H               | H               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.6 (2H, m), 2.86 (2H, t, J = 5.4Hz), 3.32 (2H, d, J = 3.2Hz), 3.4-3.5 (2H, m), 6.10 (1H, m), 6.58 (1H, d, J = 11.6Hz), 7.0-7.8 (9H, m), 8.27 (1H, d, J = 7.8Hz)<br>Mass: 344 (M <sup>+</sup> +H)               |

**Example 34**

The following compounds are prepared in a similar manner to that of Example 9. If necessary, the starting compounds of them were prepared in similar manners of Preparation 5, Preparation 17 and Preparation 20.

5



| No. | X  | R <sup>18</sup> | R <sup>24</sup> |   |
|-----|----|-----------------|-----------------|---|
| (1) | CH | Cl              | Cl              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.6 (7H, m), 3.0-3.3 (2H, m), 3.3-3.5 (2H, m), 6.62 (1H, d, J = 12Hz), 7.0-7.5 (6H, m), 7.82 (1H, dd, J = 8.0, 1.4Hz), 8.20 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 415 (M <sup>+</sup> +H)               |
| (2) | CH | Cl              | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.8 (7H, m), 3.1-3.3 (2H, m), 3.3-3.5 (2H, m), 6.62 (1H, d, J = 12Hz), 7.0-7.6 (6H, m), 7.84 (1H, dd, J = 8.0, 1.4Hz), 8.20 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 448 (M <sup>+</sup> +H)               |
| (3) | CH | Cl              | OMe             | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.8 (7H, m), 3.1-3.3 (2H, m), 3.3-3.5 (2H, m), 3.79 (3H, s), 6.59 (1H, d, J = 12Hz), 6.8-7.4 (6H, m), 7.84 (1H, dd, J = 8.0, 1.4Hz), 8.20 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 410 (M <sup>+</sup> +H) |
| (4) | CH | Me              | CF <sub>3</sub> | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.8 (7H, m), 2.64 (3H, s), 3.1-3.3 (2H, m), 3.3-3.5 (2H, m), 6.54 (1H, d, J = 12Hz), 7.0-7.4 (7H, m), 8.15 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 428 (M <sup>+</sup> +H)                                |
| (5) | CH | Me              | OMe             | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.8 (7H, m), 2.64 (3H, s), 3.1-3.3 (2H, m), 3.3-3.5 (2H, m), 3.79 (3H, s), 6.51 (1H, d, J = 12Hz), 6.8-7.6 (7H, m), 8.16 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 390 (M <sup>+</sup> +H)                  |
| (6) | CH | Me              | Me              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.8 (7H, m), 2.32 (3H, s), 2.64 (3H, s), 3.1-3.3 (2H, m), 3.3-3.5 (2H, m), 6.51 (1H, d, J = 12Hz), 6.8-7.6 (7H, m), 8.16 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 374 (M <sup>+</sup> +H)                  |
| (7) | CH | Me              | Cl              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.8 (7H, m), 2.64 (3H, s), 3.1-3.3 (2H, m), 3.3-3.5 (2H, m), 6.51 (1H, d, J = 12Hz), 6.8-7.6 (7H, m), 8.16 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 394 (M <sup>+</sup> +H)                                |
| (8) | CH | Me              | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.8 (7H, m), 2.64 (3H, s), 3.1-3.3 (2H, m), 3.3-3.5 (2H, m), 6.51 (1H, d, J = 12Hz), 6.8-7.6 (7H, m), 8.20 (1H, dd, J = 8.0, 1.4Hz)<br>Mass: 367 (M <sup>+</sup> +H)                                |
| (9) | N  | Me              | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.63 (3H, s), 2.7-2.9 (2H, m), 3.1-3.3 (2H, m), 3.4-3.6 (2H, m), 6.58 (1H, d, J = 16.2Hz), 6.8-7.6 (6H, m), 7.60 (1H, d, J = 7.0Hz), 8.15 (1H, dd, J = 7.0, 1.4Hz)<br>Mass: 378 (M <sup>+</sup> +H)     |



| No.  | X | R <sup>18</sup> | R <sup>24</sup> |  |
|------|---|-----------------|-----------------|--|
| (10) | N | Me              | CN              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.3-2.8 (7H, m), 3.2-3.5 (6H, m), 6.45 (1H, d, J = 15Hz), 6.8-7.8 (7H, m), 7.91 (1H, d, J = 8Hz)<br>Mass: 386 (M <sup>+</sup> +H)  |
| (11) | N | Me              | Cl              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.3-2.8 (7H, m), 3.2-3.5 (6H, m), 6.45 (1H, d, J = 15Hz), 6.8-7.8 (7H, m), 7.91 (1H, d, J = 8Hz)<br>Mass: 395 (M <sup>+</sup> +H)  |
| (12) | N | Cl              | Cl              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (4H, m), 3.2-3.4 (4H, m), 3.4-3.6 (2H, m), 6.62 (1H, d, J = 16Hz), 6.81 (2H, d, J = 8Hz), 7.1-7.4 (4H, m), 7.84 (1H, dd, J = 8, 1.2Hz), 8.20 (1H, dd, J = 8, 1.2Hz)<br>Mass: 416 (M <sup>+</sup> +H) |
| (13) | N | Cl              | F               | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (4H, m), 3.2-3.4 (4H, m), 3.4-3.6 (2H, m), 6.64 (1H, d, J = 16Hz), 6.7-7.4 (6H, m), 7.84 (1H, dd, J = 8, 1.2Hz), 8.21 (1H, dd, J = 8, 1.2Hz)<br>Mass: 399 (M <sup>+</sup> +H)                        |
| (14) | N | Cl              | CN              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (4H, m), 3.2-3.4 (4H, m), 3.4-3.6 (2H, m), 6.62 (1H, d, J = 16Hz), 6.7-7.4 (6H, m), 7.84 (1H, dd, J = 8, 1.2Hz), 8.20 (1H, dd, J = 8, 1.2Hz)<br>Mass: 406 (M <sup>+</sup> +H)                        |
| (15) | N | H               | Cl              | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.5-2.7 (4H, m), 3.2-3.4 (4H, m), 3.4-3.6 (2H, m), 6.52 (1H, d, J = 16Hz), 6.7-7.4 (8H, m), 8.28 (1H, dd, J = 8, 1.2Hz)<br>Mass: 381 (M <sup>+</sup> +H)   |

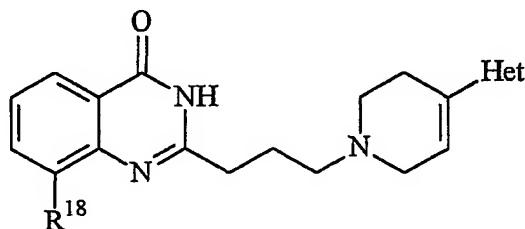
Example 35

The following compounds are prepared in a similar manner to that of Example 9.

If necessary, the starting compounds of them were prepared in similar manners of

5 Preparation 17 and Preparation 20

10



15

| No. | R <sup>18</sup> | Het                       |  |
|-----|-----------------|---------------------------|--|
| (1) | H               | 1,3-thiazol-2-yl          | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.06 (2H, quint., J=6.4 Hz), 2.67 (2H, t, J=6.1 Hz), 2.8-3.0 (6H, m), 3.34 (2H, d, J=3.3 Hz), 6.62 (1H, t, J=3.7 Hz), 7.23 (1H, d, J=3.3 Hz), 7.41 (1H, t, J=7.3 Hz), 7.6-7.7 (2H, m), 7.77 (1H, d, J=3.3 Hz), 8.22 (1H, d, J=3.9 Hz), 12.22 (1H, br).<br>Mass (APCI): 352.93 (M <sup>+</sup> +H)                              |
| (2) | H               | 1-methyl-1H-imidazol-2-yl | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=6.0 Hz), 2.69 (2H, t, J=5.9 Hz), 2.8-3.0 (6H, m), 3.32 (2H, d, J=3.2 Hz), 3.79 (3H, s), 5.97 (1H, t, J=3.4 Hz), 6.86 (1H, d, J=1.1 Hz), 7.02 (1H, d, J=1.1 Hz), 7.41 (1H, t, J=8.1 Hz), 7.63 (1H, d, J=6.9 Hz), 7.71 (1H, t, J=8.2 Hz), 8.20 (1H, d, J=8.0 Hz).<br>Mass (APCI): 349.93 (M <sup>+</sup> +H) |
| (3) | H               | 1-methyl-1H-pyrazol-5-yl  | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=5.9 Hz), 2.69 (4H, t, J=5.8 Hz), 2.8-3.0 (4H, m), 3.31 (2H, q, J=3.1 Hz), 3.97 (3H, s), 5.89 (1H, br s), 6.20 (1H, d, J=1.9 Hz), 7.42 (1H, t, J=7.3 Hz), 7.43 (1H, d, J=1.8 Hz), 7.63 (1H, d, J=7.0 Hz), 7.72 (1H, t, J=6.8 Hz), 8.23 (1H, d, J=8.0 Hz).<br>Mass (APCI): 350.00 (M <sup>+</sup> +H)        |
| (4) | H               | 2-thienyl                 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.04 (2H, quint., J=6.3 Hz), 2.64 (2H, t, J=6.1 Hz), 2.8-3.0 (6H, m), 3.28 (2H, d, J=3.2 Hz), 6.12 (1H, br s), 6.9-7.1 (2H, m), 7.15 (1H, d, J=4.9 Hz), 7.42 (1H, t, J=8.1 Hz), 7.63 (1H, d, J=6.9 Hz), 7.72 (1H, t, J=6.7 Hz), 8.23 (1H, d, J=8.0 Hz).<br>Mass (APCI): 351.87 (M <sup>+</sup> +H)                             |
| (5) | Cl              | 2-thienyl                 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.05 (2H, quint., J=6.0 Hz), 2.67 (2H, t, J=5.9 Hz), 2.8-3.0 (6H, m), 3.31 (2H, d, J=3.4 Hz), 6.12 (1H, t, J=3.5 Hz), 6.9-7.1 (2H, m), 7.15 (1H, d, J=4.9 Hz), 7.31 (1H, t, J=7.8 Hz), 7.78 (1H, d, J=7.7 Hz), 8.14 (1H, d, J=7.9 Hz).<br>Mass (APCI): 385.80 (M <sup>+</sup> +H)  |
| (6) | H               | 3-thienyl                 | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.04 (2H, quint., J=5.1 Hz), 2.64 (2H, t, J=6.0 Hz), 2.7-3.0 (6H, m), 3.29 (2H, d, J=3.3 Hz), 6.11 (1H, br s), 7.1-7.3 (3H, m), 7.41 (1H, t, J=8.1 Hz), 7.6-7.8 (2H, m), 8.23 (1H, d, J=8.4 Hz), 12.47 (1H, br).<br>Mass (APCI): 352.13 (M <sup>+</sup> +H)  |
| (7) | Cl              | 3-thienyl                 | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.97 (2H, quint., J=7.0 Hz), 2.39 (2H, br), 2.4-2.5 (2H, m), 2.61 (2H, t, J=5.3 Hz), 2.73 (2H, t, J=7.3 Hz), 3.06 (2H, d, J=3.1 Hz), 6.01 (1H, br s), 6.9-7.1 (2H, m), 7.34 (1H, d, J=6.3 Hz), 7.38 (1H, t, J=7.8 Hz), 7.91 (1H, d, J=7.8 Hz), 7.99 (1H, d, J=7.9 Hz).<br>Mass (API-ES): 386.2 (M <sup>+</sup> +H)           |

| No.  | R <sup>18</sup> | Het                |   |
|------|-----------------|--------------------|---|
| (8)  | H               | 4-methyl-2-thienyl | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.04 (2H, quint., J=6.3 Hz), 2.22 (3H, s), 2.63 (2H, t, J=6.1 Hz), 2.7-3.0 (6H, m), 3.26 (2H, d, J=3.3 Hz), 6.07 (1H, t, J=3.6 Hz), 6.71 (1H, s), 6.83 (1H, s), 7.41 (1H, t, J=7.3 Hz), 7.5-7.8 (2H, m), 8.23 (1H, d, J=7.8 Hz)<br>Mass (APCI): 366.00 (M <sup>+</sup> +H)  |
| (9)  | H               | 5-acetyl-2-thienyl | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.94 (2H, quint., J=7.0 Hz), 2.3-2.7 (11H, m), 3.08 (2H, br s), 6.31 (1H, br s), 7.15 (1H, d, J=3.9 Hz), 7.42 (1H, t, J=7.1 Hz), 7.59 (1H, d, J=8.0 Hz), 7.76 (1H, t, J=7.1 Hz), 7.82 (1H, d, J=4.0 Hz), 8.04 (1H, d, J=7.8 Hz), 12.19 (1H, br s)<br>Mass (APCI): 394.00 (M <sup>+</sup> +H)                          |
| (10) | H               | 5-chloro-2-thienyl | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.93 (2H, quint., J=7.3 Hz), 2.3-2.7 (8H, m), 3.04 (2H, d, J=2.9 Hz), 5.98 (1H, br s), 6.87 (1H, d, J=3.9 Hz), 7.01 (1H, d, J=3.9 Hz), 7.43 (1H, t, J=7.5 Hz), 7.59 (1H, d, J=7.5 Hz), 7.76 (1H, t, J=7.1 Hz), 8.05 (1H, d, J=7.9 Hz), 12.20 (1H, br s)<br>Mass (APCI): 385.87 (M <sup>+</sup> +H)                    |
| (11) | H               | 5-cyano-2-thienyl  | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.94 (2H, quint., J=7.2 Hz), 2.3-2.8 (8H, m), 3.09 (2H, d, J=2.9 Hz), 6.31 (1H, s), 7.20 (1H, d, J=3.9 Hz), 7.42 (1H, t, J=7.5 Hz), 7.58 (1H, d, J=7.7 Hz), 7.76 (1H, t, J=7.6 Hz), 7.86 (1H, d, J=4.0 Hz), 8.04 (1H, d, J=7.9 Hz), 12.19 (1H, br)  |
| (12) | H               | 5-methyl-2-thienyl | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.03 (2H, quint., J=6.3 Hz), 2.45 (3H, s), 2.63 (2H, t, J=6.1 Hz), 2.7-3.0 (6H, m), 3.26 (2H, d, J=3.1 Hz), 5.97 (1H, br s), 6.62 (1H, d, J=3.5 Hz), 6.79 (1H, d, J=3.5 Hz), 7.41 (1H, t, J=7.3 Hz), 7.63 (1H, d, J=7.0 Hz), 7.71 (1H, t, J=6.8 Hz), 8.23 (1H, d, J=7.8 Hz)<br>Mass (APCI): 365.93 (M <sup>+</sup> +H)  |
| (13) | H               | 2-pyridinyl        | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.06 (2H, quint., J=6.1 Hz), 2.68 (2H, t, J=6.0 Hz), 2.8-3.0 (6H, m), 3.37 (2H, d, J=3.9 Hz), 6.69 (1H, t, J=3.4 Hz), 7.16 (1H, dd, J=7.4, 4.8 Hz), 7.3-7.5 (2H, m), 7.6-7.8 (3H, m), 8.22 (1H, d, J=7.8 Hz), 8.57 (1H, d, J=3.9 Hz)<br>Mass (API-ES): 347.2 (M <sup>+</sup> +H)  |
| (14) | H               | 3-pyridinyl        | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.06 (2H, quint., J=6.1 Hz), 2.68 (2H, t, J=5.9 Hz), 2.8-3.0 (6H, m), 3.32 (2H, d, J=3.2 Hz), 6.15 (1H, br s), 7.28 (1H, dd, J=7.9, 4.9 Hz), 7.41 (1H, t, J=7.3 Hz), 7.6-7.8 (3H, m), 8.22 (1H, d, J=7.9 Hz), 8.50 (1H, d, J=4.8 Hz), 8.71 (1H, d, J=2.1 Hz), 12.60 (1H, br)<br>Mass (APCI): 347.13 (M <sup>+</sup> +H) |
| (15) | Cl              | 4-pyridinyl        | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.9-2.1 (2H, m), 2.37 (2H, s), 2.45-2.8 (6H, m), 3.10 (2H, d, J=2.8 Hz), 6.15 (1H, s), 7.3-7.4 (3H, m), 7.90 (1H, dd, J=7.8, 1.4 Hz), 7.97 (1H, dd, J=7.8, 1.4 Hz), 8.3-8.4 (2H, m), 12.44 (1H, br s)   |

| No.  | R <sup>18</sup> | Het         |   |
|------|-----------------|-------------|---|
| (16) | H               | 4-pyridinyl | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.06 (2H, quint., J=6.1 Hz), 2.68 (2H, t, J=6.0 Hz), 2.7-3.0 (6H, m), 3.33 (2H, d, J=3.3 Hz), 6.33 (1H, br s), 7.33 (2H, d, J=6.2 Hz), 7.41 (1H, t, J=7.4 Hz), 7.64 (1H, d, J=7.0 Hz), 7.72 (1H, t, J=7.5 Hz), 8.22 (1H, d, J=7.9 Hz), 8.57 (2H, d, J=6.2 Hz), 12.49 (1H, br)<br>Mass (API-ES): 347.3 (M <sup>+</sup> +H) |

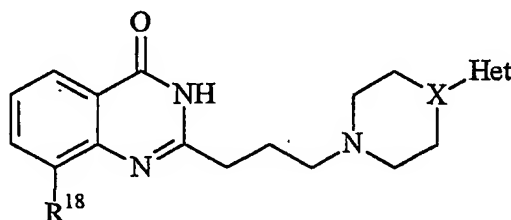
**Example 36**

The following compounds are prepared in a similar manner to that of Example 9.

If necessary, the starting compounds of them were prepared in similar manners of

5 Preparation 17 and Preparation 20.

10



| No. | R <sup>18</sup> | X  | Het                      |   |
|-----|-----------------|----|--------------------------|---|
| (1) | H               | CH | 1-methyl-1H-pyrazol-5-yl | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.0 (4H, m), 2.1-2.4 (4H, m), 2.5-2.7 (3H, m), 2.8-3.0 (2H, m), 3.1-3.3 (2H, m), 6.32 (1H, br s), 7.3-7.5 (2H, m), 7.63 (1H, d, J=6.9 Hz), 7.72 (1H, t, J=6.8 Hz), 8.27 (1H, d, J=7.7 Hz)<br>Mass (APCI): 361.93 (M <sup>+</sup> +H)                  |
| (2) | H               | CH | 2-thienyl                | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.9-2.4 (8H, m), 2.58 (2H, t, J=5.7 Hz), 2.8-3.0 (3H, m), 3.14 (2H, br d, J=5.0 Hz), 6.9-7.0 (2H, m), 7.15 (1H, d, J=6.3 Hz), 7.42 (1H, t), 7.6-7.8 (2H, m), 8.27 (1H, d, J=7.8 Hz)<br>Mass (APCI-ES): 354.3 (M <sup>+</sup> +H)                          |
| (3) | H               | CH | 3-Thienyl                | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.0 (4H, m), 2.2-2.4 (4H, m), 2.5-2.6 (2H, m), 2.6-2.8 (1H, m), 2.9-3.0 (2H, m), 3.16 (2H, br d, J=5.4 Hz), 7.1-7.3 (3H, m), 7.42 (1H, t), 7.6-7.8 (2H, m), 8.27 (1H, d, J=7.9 Hz)<br>Mass (APCI): 354.13 (M <sup>+</sup> +H)                         |
| (4) | H               | CH | 4-methyl-2-thienyl       | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.9-2.3 (11H, m), 2.56 (2H, t, J=5.7 Hz), 2.7-3.0 (3H, m), 3.12 (2H, br d, J=7.3 Hz), 6.71 (1H, s), 6.77 (1H, s), 7.42 (1H, t, J=7.4 Hz), 7.62 (1H, d, J=7.1 Hz), 7.71 (1H, t, J=6.7 Hz), 8.26 (1H, d, J=8.0 Hz)<br>MS (APCI): 368.20 (M <sup>+</sup> +H) |

| No.  | R <sup>18</sup> | X  | Het                |  |
|------|-----------------|----|--------------------|--|
| (5)  | H               | CH | 5-methyl-2-thienyl | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.9-2.3 (8H, m), 2.45 (3H, s), 2.56 (2H, t, J=5.7 Hz), 2.7-3.0 (3H, m), 3.0-3.2 (2H, m), 6.60 (1H, d, J=3.3 Hz), 6.73 (1H, d, J=3.3 Hz), 7.41 (1H, t, J=7.3 Hz), 7.5-7.8 (2H, m), 8.27 (1H, d, J=8.0 Hz)<br>Mass (APCI): 368.13 (M <sup>+</sup> +H)  |
| (6)  | H               | CH | 4-pyridinyl        | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.87 (2H, br d, J=11.1 Hz), 1.99 (2H, quint., J=5.5 Hz), 2.1-2.4 (4H, m), 2.4-2.7 (3H, m), 2.9-3.0 (2H, m), 3.23 (2H, br d, J=9.4 Hz), 7.38 (2H, d, J=6.1 Hz), 7.44 (1H, t, J=8.9 Hz), 7.63 (1H, d), 7.72 (1H, t, J=6.8 Hz), 8.30 (1H, d, J=8.4 Hz), 8.57 (1H, d, J=6.1 Hz)<br>Mass (APCI): 348.87 (M <sup>+</sup> +H) |
| (7)  | H               | N  | 2-pyridinyl        | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.3-3.4 (4H, m), 7.40 (1H, t, J = 8Hz), 7.48 (1H, d, J = 8Hz), 7.7-8.2 (4H, m), 8.26 (1H, d, J = 1.2Hz)<br>Mass: 350(M+1)  |
| (8)  | Cl              | N  | 2-pyridinyl        | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.8 (8H, m), 3.1-3.4 (2H, m), 6.61 (1H, m), 7.2-8.0 (6H, m), 8.51 (1H, m)<br>Mass: 381(M <sup>+</sup> +H)   |
| (9)  | H               | N  | 4-pyridinyl        | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.2-3.4 (4H, m), 6.76 (2H, d, J = 8Hz), 7.42 (1H, t, J = 8Hz), 7.58 (1H, d, J = 8Hz), 7.72 (1H, t, J = 8Hz), 8.1-8.3 (3H, m)<br>Mass: 350 (M <sup>+</sup> +H)  |
| (10) | Cl              | N  | 4-pyridinyl        | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.8 (8H, m), 3.1-3.4 (2H, m), 6.41 (1H, m), 7.3-7.5 (2H, m), 7.78 (1H, d, J = 8Hz), 7.91 (1H, d, J = 8Hz), 8.3-8.6 (2H, m)<br>Mass: 381(M <sup>+</sup> +H)  |
| (11) | H               | N  | 2-pyrazinyl        | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 1.7-2.0 (2H, m), 2.3-2.7 (8H, m), 3.3-3.4 (4H, m), 7.40 (1H, t, J = 8Hz), 7.48 (1H, d, J = 8Hz), 7.7-8.2 (3H, m), 8.26 (1H, d, J = 1.2Hz)<br>Mass: 351(M <sup>+</sup> +H)  |

### Example 37

The following compounds are prepared in a similar manner to that of Example 25.

- 5 (1) 8-Chloro-2-{3-[4-(2-thienyl)-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone hydrochloride

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.1-2.4 (2H, m), 2.7-2.9 (4H, m), 3.1-3.4 (2H, m), 3.4-3.8 (3H, m), 3.9-4.1 (1H, m), 6.10 (1H, br s), 7.07 (1H, d, J=3.6 Hz), 7.20 (1H, d, J=3.6 Hz), 7.4-7.6 (2H, m), 7.95 (1H, d, J=7.8 Hz), 8.06 (1H, d, J=7.8 Hz),

10.20 (1H, br), 12.51 (1H, br s)

Mass (APCI): 385.80 ( $M^+ + H$ )

- (2) 8-Chloro-2-{3-[4-(3-thienyl)-3,6-dihydro-1(2H)-pyridinyl]propyl}-  
4(3H)-quinazolinone hydrochloride

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.21 (2H, quint., J=8.2 Hz), 2.79 (4H, t, J=6.8 Hz), 3.1-3.4 (3H, m), 3.7-3.9 (2H, m), 3.9-4.1 (1H, m), 6.09 (1H, br s), 7.07 (1H, dd, J=7.0, 3.6 Hz), 7.19 (1H, d, J=3.0 Hz), 7.4-7.6 (2H, m), 7.95 (1H, d, J=7.8 Hz), 8.06 (1H, d, J=7.9 Hz), 10.53 (1H, br), 12.52 (1H, br s)

Mass (APCI): 385.80 ( $M^+ + H$ )

- 10 (3) 8-Chloro-2-{3-[4-(4-pyridinyl)-3,6-dihydro-1(2H)-pyridinyl]propyl}-  
4(3H)-quinazolinone dihydrochloride

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, δ): 6.79 (1H, s), 7.45 (1H, t, J=7.9 Hz), 7.87 (2H, d, J=6.6 Hz), 7.94 (1H, dd, J=7.9, 1.4 Hz), 8.06 (1H, dd, J=7.9, 1.4 Hz), 8.77 (2H, d, J=6.6 Hz), 12.52 (1H, br s)

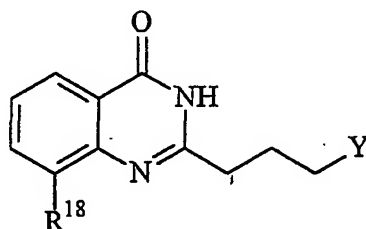
15

#### Example 38

The following compounds are prepared in a similar manner to that of Example 9.

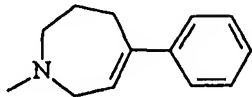
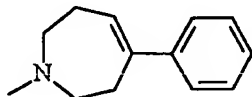
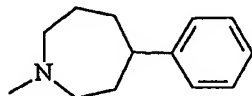
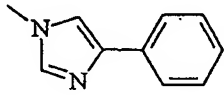
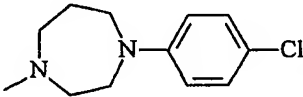
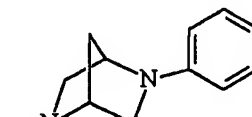
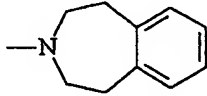
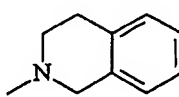
If necessary, the starting compounds of them were prepared in similar manners of Preparation 17 and Preparation 20.

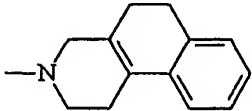

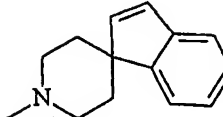
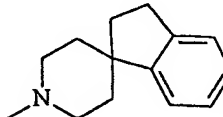
20



25

| No. | R18 | Y |  |
|-----|-----|---|--|
| (1) | H   |   | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.1 (2H, m), 2.4-3.0 (6H, m), 3.17 (2H, s), 3.55 (2H, t, J=5.3 Hz), 7.2-8.0 (8H, m), 12.21 (1H, brs)<br>Mass (APCI): 419.2 ( $M^+ + Na$ )  |
| (2) | H   |   | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.0-2.2 (3H, m), 2.4-2.7 (1H, m), 2.79 (1H, t, J=9.8 Hz), 2.8-3.0 (5H, m), 3.27 (1H, q, J=9.7 Hz), 3.48 (1H, t, J=8.8 Hz), 3.72 (1H, quint., J=8.7 Hz), 7.1-7.5 (6H, m), 7.62 (1H, d, J=6.8 Hz), 7.70 (1H, t, J=6.8 Hz), 8.21 (1H, d, J=7.9 Hz)<br>Mass (APCI): 334.20 ( $M^+ + H$ ) |

| No.  | R18 | Y |  |
|------|-----|---|--|
| (3)  | H   |   |  <p><sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 1.8-2.1 (4H, m), 2.73 (2H, t, J=5.9 Hz), 2.8-2.9 (4H, m), 3.15 (2H, t, J=5.6 Hz), 3.52 (2H, d, J=6.2 Hz), 6.01 (1H, t, J=6.2 Hz), 7.1-7.5 (6H, m), 7.6-7.8 (2H, m), 8.25 (1H, d, J=7.8 Hz)<br/>Mass (APCI): 360.07 (M<sup>+</sup>+H)</p>                 |
| (4)  | H   |   |  <p><sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 1.99 (2H, quint., J=5.3 Hz), 2.6-2.8 (2H, m), 2.8-3.1 (10H, m), 6.15 (1H, t, J=6.1 Hz), 7.2-7.5 (6H, m), 7.6-7.8 (2H, m), 8.25 (1H, d, J=7.4 Hz)<br/>Mass (APCI): 360.07 (M<sup>+</sup>+H)</p>   |
| (5)  | H   |   |  <p><sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 1.4-2.3 (10H, m), 2.8-3.1 (7H, m), 7.1-7.4 (5H, m), 7.42 (1H, t, J=7.9 Hz), 7.6-7.8 (2H, m), 8.28 (1H, d, J=7.8 Hz)<br/>Mass (APCI): 362.20 (M<sup>+</sup>+H)</p>  |
| (6)  | H   |   |  <p><sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.24 (2H, quint., J=7.2 Hz), 2.62 (2H, t, J=7.4 Hz), 4.10 (2H, t, J=6.8 Hz), 7.18 (1H, t), 7.34 (2H, t, J=7.4 Hz), 7.46 (1H, t), 7.68 (1H, d), 7.7-7.9 (5H, m), 8.08 (1H, d, J=6.7 Hz), 12.19 (1H, br s)<br/>Mass (APCI): 331.07 (M<sup>+</sup>+H)</p> |
| (7)  | H   |   |  <p><sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.0 (4H, m), 2.3-2.7 (10H, m), 6.65 (2H, d, J = 8Hz), 7.02 (2H, d, J = 8Hz), 7.41 (1H, t, J = 8Hz), 7.61 (1H, d, J = 8Hz), 7.72 (1H, t, J = 8Hz), 8.08 (1H, d, J = 8Hz)<br/>Mass: 397 (M<sup>+</sup>+H)</p>                                      |
| (8)  | H   |   |  <p><sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.0 (2H, m), 2.4-3.2 (12H, m), 6.6-6.8 (2H, m), 6.8-7.0 (2H, m), 7.3-7.8 (3H, m), 8.06 (1H, m)<br/>Mass: 379 (M<sup>+</sup>+H)</p>   |
| (9)  | Cl  |   |  <p><sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.0 (2H, m), 2.3-2.8 (12H, m), 7.06 (4H, m), 7.39 (1H, t, J = 8Hz), 7.91 (1H, d, J = 8Hz), 8.02 (1H, d, J = 8Hz)<br/>Mass: 368 (M<sup>+</sup>+H)</p>   |
| (10) | Me  |   |  <p><sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.0 (2H, m), 2.52 (3h, s), 2.4-2.8 (10H, m), 7.1-7.3 (4H, m), 7.31 (1H, t, J = 8Hz), 7.62 (1H, d, J = 8Hz), 7.91 (1H, d, J = 8Hz)<br/>Mass: 334 (M<sup>+</sup>+H)</p>  |

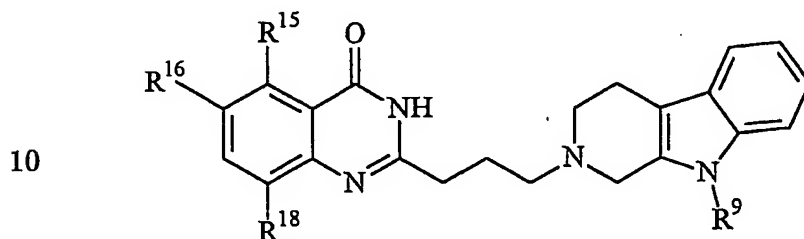
| No.  | R18 | Y   |   |
|------|-----|---|---|
| (11) | H   |    | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 2.06 (2H, quint., J=6.4 Hz), 2.20 (2H, t, J=7.9 Hz), 2.65 (2H, t, J=6.2 Hz), 2.7-3.0 (8H, m), 3.20 (2H, br s), 7.1-7.3 (4H, m), 7.41 (1H, t, J=7.3 Hz), 7.63 (1H, d, J=6.9 Hz), 7.72 (1H, t, J=7.4 Hz), 8.22 (1H, d, J=7.8 Hz)<br>Mass (API-ES): 372.3 (M <sup>+</sup> +H)  |
| (12) | H   |    | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.8-2.1 (4H, m), 2.1-2.4 (4H, m), 2.4-2.6 (3H, m), 2.8-2.9 (7H, m), 7.13 (4H, t, J=4.9 Hz), 7.42 (1H, t, J=6.8 Hz), 7.63 (1H, d, J=7.0 Hz), 7.72 (1H, t, J=6.8 Hz), 8.22 (1H, d, J=7.8 Hz)<br>Mass (APCI): 373.87 (M <sup>+</sup> +H)   |
| (13) | H   |    | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.45 (2H, br d, J=14.7 Hz), 2.03 (2H, quint., J=5.5 Hz), 2.4-2.8 (6H, m), 2.9-3.1 (2H, m), 3.20 (2H, br d, J=11.5 Hz), 6.79 (1H, d, J=5.7 Hz), 6.91 (1H, d, J=5.7 Hz), 7.2-7.4 (3H, m), 7.45 (1H, t, J=6.6 Hz), 7.65 (1H, t, J=6.9 Hz), 7.73 (1H, t, J=6.8 Hz), 7.87 (1H, d, J=7.2 Hz), 8.33 (1H, d, J=7.9 Hz), 14.18 (1H, br)<br>Mass (APCI): 372.07 (M <sup>+</sup> +H) |
| (14) | H   |  | <sup>1</sup> H NMR (200MHz, CDCl <sub>3</sub> , δ): 1.65 (2H, br s), 1.97 (2H, quint., J=5.4 Hz), 2.06 (2H, t, J=7.4 Hz), 2.2-2.6 (4H, m), 2.62 (2H, t, J=7.5 Hz), 2.8-3.1 (6H, m), 7.1-7.4 (3H, m), 7.43 (1H, t, J=8.1 Hz), 7.6-7.8 (3H, m), 8.31 (1H, d, J=7.9 Hz)<br>Mass (APCI): 374.13 (M <sup>+</sup> +H)   |

**Example 39**

The following compounds are prepared in a similar manner to that of **Example 9**.

If necessary, the starting compounds of them were prepared in similar manners of

5 **Preparation 17** and **Preparation 20**.





| No. | R <sup>15</sup> | R <sup>16</sup> | R <sup>18</sup> | R <sup>29</sup> |   |
|-----|-----------------|-----------------|-----------------|-----------------|---|
| (1) | H               | H               | Cl              | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H,m), 2.5-2.8 (6H,m), 6.95 (1H, t, J = 8Hz), 7.2-7.4 (4H, m), 7.79 (1H, d, J = 8Hz), 7.95 (1H, d, J = 8Hz)<br>Mass: 393 (M <sup>+</sup> +H)                         |
| (2) | H               | H               | Me              | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H,m), 2.5-2.8 (8H,m), 3.62 (2H, m), 6.8-7.4 (5H, m), 7.62 (1H, d, J = 8Hz), 7.90 (1H, d, J = 8Hz)<br>Mass: 373 (M <sup>+</sup> +H)                                  |
| (3) | H               | H               | Me              | Me              | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H,m), 2.5-2.8 (8H,m), 2.52 (3H,s), 3.58 (3H, s), 6.8-7.4 (5H, m), 7.60 (1H, d, J = 8Hz), 7.88 (1H, d, J = 8Hz)<br>Mass: 387 (M <sup>+</sup> +H)                     |
| (4) | H               | H               | OMe             | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H,m), 2.5-2.8 (8H,m), 3.89 (3H, s), 6.8-7.5 (6H, m), 7.62 (1H, d, J = 8Hz)<br>Mass: 389 (M <sup>+</sup> +H)   |
| (5) | Cl              | H               | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H,m), 2.5-2.8 (6H,m), 3.0-3.2 (2H, m), 6.8-7.7 (7H, m)<br>Mass: 393 (M <sup>+</sup> +H)   |
| (6) | H               | Cl              | H               | H               | <sup>1</sup> H NMR (200MHz, DMSO-d <sub>6</sub> , δ): 2.0-2.2 (2H,m), 2.5-2.8 (6H,m), 3.0-3.2 (2H, m), 6.8-7.3 (4H, m), 7.62 (1H, d, J = 8Hz), 7.78 (1H, dd, J = 8, 1.2Hz), 7.96 (1H,d, J = 1.2Hz)<br>Mass: 393 (M <sup>+</sup> +H) |

Example 40

The following compounds are prepared in a similar manner to that of Example 9.

If necessary, the starting compounds of them were prepared in similar manners of

5 Preparation 17 and Preparation 20.

- (1) 2-[(1-ethyl-3-azetidiny)methyl]-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, CDCl<sub>3</sub>, δ): 1.04 (3H, t, J = 7Hz), 2.5-3.3 (9H, m), 7.4-8.2 (4H, m)  
Mass: 244 (M<sup>+</sup>+H)
- 10 (2) 2-[(1-ethyl-3-pyrrolidinyl)methyl]-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.06 (3H, t, J = 8Hz), 2.2-2.8 (7H, m), 7.4-8.2 (4H, m)  
Mass: 258 (M<sup>+</sup>+H)
- 15 (3) 2-[[1-(3-phenylpropyl)-3-pyrrolidinyl]methyl]-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.6-1.9 (2H, m), 2.1-2.8 (10H, m), 7.0-7.3 (5H, m), 7.48 (1H, t, J = 8Hz), 7.59 (1H, d, J = 8Hz), 7.75 (1H, t, J = 8Hz), 8.11 (1H, d, J = 8Hz)  
Mass: 348(M<sup>+</sup>+H)

- (4) 2-[(1-ethyl-4-piperidyl)methyl]-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 0.95 (3H, t, J = 7Hz), 1.5-2.2 (4H, m), 2.32 (2H, q, J = 7Hz), 7.41 (1H, t, J = 8Hz), 7.52 (1H, d, J = 8Hz), 7.80 (1H, t, J = 8Hz), 8.08 (1H, d, J = 8Hz)  
5 Mass: 272 (M<sup>+</sup>+H)
- (5) 2-{3-[4-ethynyl-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.7-2.2 (4H, m), 2.5-2.7 (2H, m), 2.7-2.9 (2H, m), 6.04 (1H, m), 7.40 (1H, t, J = 8Hz), 7.57 (1H, d, J = 8Hz), 7.75 (1H, t, J = 8Hz), 8.06 (1H, d, J = 8Hz)  
10 Mass: 294 (M<sup>+</sup>+H)
- (6) 2-{3-[4-phenylethynyl-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.0 (2H, m), 2.6-2.8 (4H, m), 3.78 (2H, s), 7.2-8.2 (11H, m)  
Mass: 413 (M<sup>+</sup>+H)
- 15 (7) 2-{3-[4-(1-naphthylmethyl)-1-piperazinyl]propyl}-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.7-2.0 (2H, m), 2.2-2.4 (2H, m), 2.5-2.8 (6H, m), 3.0-3.2 (2H, m), 6.12 (1H, m), 7.3-7.5 (6H, m), 7.59 (1H, d, J = 8Hz), 7.77 (1H, t, J = 8Hz), 8.06 (1H, d, J = 8Hz)  
Mass: 370 (M<sup>+</sup>+H)
- 20 (8) 2-{3-[4-(ethylsulfonyl)-1-piperazinyl]propyl}-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.14 (3H, t, J = 7.5Hz), 1.8-2.0 (2H, m), 2.5-2.8 (4H, m), 2.99 (2H, q, J = 7.5Hz), 3.0-3.3 (4H, m), 7.40 (1H, t, J = 8Hz), 7.52 (1H, d, J = 8Hz), 7.75 (1H, t, J = 8Hz), 8.09 (1H, d, J = 8Hz)  
Mass: 365 (M<sup>+</sup>+H)
- 25 (9) 2-{3-[4-(2-furoyl)-1-piperazinyl]propyl}-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.0 (2H, m), 2.2-2.8 (8H, m), 6.6-6.7 (1H, m), 6.9-7.0 (1H, m), 7.48 (1H, t, J = 8Hz), 7.68 (1H, d, J = 8Hz), 7.7-7.9 (2H, m), 8.09 (1H, m)  
Mass: 367 (M<sup>+</sup>+H)
- 30 (10) 2-[3-(4-benzoyl-1-piperidyl)propyl]-4(3H)-quinazolinone  
<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.4-3.0 (15H, m), 7.4-7.9 (6H, m), 7.92 (2H, d, J = 8Hz), 8.06 (1H, d, J = 8Hz)  
Mass: 376 (M<sup>+</sup>+H)
- 35 (11) 2-[3-(4-Phenyl-3,6-dihydro-1(2H)-pyridinyl)butyl]-4(3H)-quinazolinone  
Mass (ESI): 360.3 (M<sup>+</sup>+H)

Example 41

The following compounds are prepared in a similar manner to that of Example 25. If necessary, the starting compounds of them were prepared in similar manners of Preparation 17, Preparation 20, preparation 23-(2) and Example 9.

- 5 (1) 2-(3-azetidinylmethyl)-4(3H)-quinazolinone hydrochloride  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 2.8-3.8 (5H, m), 7.4-8.2 (4H, m)  
 Mass: 202 ( $M^+ + H$ )
- (2) 2-(3-pyrrolidinylmethyl)-4(3H)-quinazolinone hydrochloride  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.6-1.9 (2H, m), 2.0-2.2 (2H, m), 2.3-3.3 (5H, m), 7.5-8.3 (4H, m)  
 10 Mass: 230 ( $M^+ + H$ )
- (3) 2-(4-piperidylmethyl)-4(3H)-quinazolinone hydrochloride  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.5-2.3 (5H, m), 2.6-3.2 (6H, m), 7.5-8.0 (3H, m), 8.15 (1H, d,  $J = 8\text{Hz}$ )  
 15 Mass: 244 ( $M^+ + H$ )

Example 42

- 2-{[5-[(Benzyloxy)carbonylamino]hexanoyl]amino}benzamide (2.8 g, 7.3 mmol) was dissolved in 1N NaOH (36.5 mL) and dioxane. The reaction mixture was stirred at  
 20 room temperature for 2 hours. The mixture was acidified with 6N HCl aqueous solution and extracted with AcOEt, washed with brine. The organic layer was dried over  $\text{MgSO}_4$  and the solvent was removed in vacuo. The obtained powder was washed with ether to give 2-{5-[(benzyloxy)carbonylamino]pentyl}-4(3H)-quinazolinone as colorless powder (1.99 g, 5.4 mmol, 75 %)
- 25  $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 1.48 (2H, t,  $J=7.9\text{ Hz}$ ), 1.60 (2H, m), 1.89 (2H, quint,  $J=7.8\text{ Hz}$ ), 2.74 (2H, t,  $J=7.6\text{ Hz}$ ), 3.25 (2H, t,  $J=6.7\text{ Hz}$ ), 4.86 (1H, br.s), 5.09 (2H, s), 7.39 (5H, m), 7.45 (1H, t,  $J=7.3\text{ Hz}$ ), 7.69 (2H, m), and 8.26 (1H, d,  $J=6.9\text{ Hz}$ )  
 Mass ( $m/z$ ): 366( $M^+ + 1$ )

30 Example 43

- 2-{5-[(Benzyloxy)carbonylamino]pentyl}-4(3H)-quinazolinone (500 mg, 1.37 mmol) and 10% Pd-C (50 mg) was suspended in THF/MeOH (1:1, 20 mL). The mixture was hydrogenated at 3 atm of hydrogen for 8 hours. After filtration of Pd-C, the solvent was removed in vacuo. The residue was washed with methanol and ether to give  
 35 2-(5-aminopentyl)-4(3H)-quinazolinone (136 mg, 0.59 mmol, 43 %) as colorless powder.  
 $^1\text{H}$  NMR (300MHz,  $\text{CDCl}_3$ ,  $\delta$ ): 1.36 (4H, s), 1.71 (2H, s), 2.51 (4H, s), 7.44 (1H, d,

J=7.0Hz), 7.58 (1H, d, J=8.5Hz), 7.76 (1H, t, J=7.7Hz), and 8.07 (1H, d, J=7.7 Hz)

#### Example 44

To a solution of 2-(5-aminopentyl)-4(3H)-quinazolinone (100mg, 0.432mmol) in 5 ethanol (5 mL) benzamide (45.9 mg, 0.432 mmol) was added. After stirring for 30 minutes at room temperature, sodium brohydride was added to the mixture, and the mixture was stirred at room temperature for 4 hours.

The reaction mixture was extracted with AcOEt and washed with saturated sodium hydrogen carbonate aqueous solution and brine. The organic layer was dried over MgSO<sub>4</sub>, 10 and the solvent was removed in vacuo. The residual colorless powder was purified with preparative TLC to give 2-(N-benzyl-5-aminopentyl)-4(3H)-quinazolinone (24 mg, 0.075 mmol, 17 %) as colorless powder.

<sup>1</sup>H NMR (300MHz, CDCl<sub>3</sub>, δ): 1.50 (2H, m), 1.61 (2H, m), 1.88 (2H, quint, J=7.6Hz), 2.66 (2H, t, J=7.0 Hz), 2.75 (2H, t, J=7.7 Hz), 3.79 (2H, s), 7.25-7.32 (5H, m), 7.45 (1H, 15 t, J=8.0 Hz), 7.68 (1H, t, J=8.1 Hz), 7.76 (1H, t, J=7.0 Hz), and 8.27 (1H, d, J=6.5Hz)

Mass (m/z): 322 (M<sup>+</sup>+1)

#### Example 45

20 The following compounds are prepared in a similar manner to those of Preparation 31, Example 42 and Example 43.

(1) 2-(3-aminopropyl)-4(3H)-quinazolinone

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 1.8-2.0 (2H, m), 2.4-3.3 (4H, m), 7.2-8.2 (4H, m)

25 Mass: 204 (M<sup>+</sup>+H)

(2) 2-(3-aminoethyl)-4(3H)-quinazolinone

<sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 2.4-2.9 (4H, m), 7.2-8.2 (4H, m)

Mass: 190 (M<sup>+</sup>+H)

(3) 2-(3-aminomethyl)-4(3H)-quinazolinone

30 <sup>1</sup>H NMR (200MHz, DMSO-d<sub>6</sub>, δ): 7.2-8.2 (4H, m)

Mass: 176 (M<sup>+</sup>+H)

#### Example 46

The following compounds are prepared in a similar manner to those of Preparation 35 31, Example 42, Example 43 and Example 25.

(1) 2-[(1E)-3-amino-3-methyl-1-butenyl]-4(3H)-quinazolinone hydrochloride

$^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.41 (3H, s), 1.64 (3H, s), 6.50 (1H, d,  $J = 16\text{Hz}$ ), 7.22 (1H, d,  $J = 16\text{Hz}$ ), 7.3-8.3 (4H, m)  
Mass: 230 ( $\text{M}^+ + \text{H}$ )

## 5 Example 47

The following compounds are prepared in a similar manner to those of Preparation 31, Example 42, Example 43 and Example 44.

- (1) 2-{3-[methyl(3-phenylpropyl)amino]propyl}-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.6-2.0 (4H, m), 2.20 (3H, m), 2.2-2.8 (8H, m),  
 10 7.0-8.0 (8H, m)  
 Mass: 336 ( $\text{M}^+ + \text{H}$ )
- (2) 2-{3-[(4-phenylbutyl)amino]propyl}-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.2-1.8 (8H, m), 2.3-2.6 (6H, m), 7.0-7.8 (9H, m), 8.07 (1H, d,  $J = 8\text{Hz}$ )  
 15 Mass: 336 ( $\text{M}^+ + \text{H}$ )
- (3) 2-{3-[(3-phenylpropyl)amino]propyl}-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.6-2.0 (4H, m), 2.3-2.7 (8H, m), 7.0-7.8 (8H, m), 8.07 (1H, d,  $J = 8\text{Hz}$ )  
 Mass: 322 ( $\text{M}^+ + \text{H}$ )
- 20 (4) 2-{3-[(2-phenylethyl)amino]propyl}-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.6-2.0 (2H, m), 2.3-2.7 (8H, m), 7.0-7.8 (8H, m), 8.08 (1H, d,  $J = 8\text{Hz}$ )  
 Mass: 308 ( $\text{M}^+ + \text{H}$ )
- (5) 8-methyl-2-{3-[(3-phenylpropyl)amino]propyl}-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.6-2.0 (4H, m), 2.45 (3H, s), 2.4-2.7 (8H, m),  
 25 7.0-7.4 (6H, m), 7.62 (1H, d,  $J = 8\text{Hz}$ ), 7.89 (1H, d,  $J = 8\text{Hz}$ )  
 Mass: 336 ( $\text{M}^+ + \text{H}$ )
- (6) 2-{3-[(4-phenoxybenzyl)amino]propyl}-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.8-2.0 (2H, m), 2.4-2.8 (4H, m), 3.66 (2H, s),  
 30 6.8-7.8 (13H, m), 8.08 (1H, d,  $J = 8\text{Hz}$ )  
 Mass: 386 ( $\text{M}^+ + \text{H}$ )
- (7) 2-{3-[(1,1'-biphenyl-3-ylmethyl)amino]propyl}-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.8-2.0 (2H, m), 2.4-2.8 (4H, m), 3.72 (2H, s),  
 7.2-7.8 (12H, m), 8.06 (1H, d,  $J = 8\text{Hz}$ )  
 35 Mass: 370 ( $\text{M}^+ + \text{H}$ )
- (8) 2-{3-[(1,1'-biphenyl-2-ylmethyl)amino]propyl}-4(3H)-quinazolinone

$^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.8-2.0 (2H, m), 2.4-2.8 (4H, m), 3.72 (2H, s), 7.2-7.8 (12H, m), 8.06 (1H, d,  $J = 8\text{Hz}$ )

Mass: 370 ( $M^+ + H$ )

- (9) 2-{3-[(1,1'-biphenyl-4-ylmethyl)amino]propyl}-4(3H)-quinazolinone  
 5  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.8-2.0 (2H, m), 2.4-2.9 (4H, m), 3.76 (2H, s), 7.2-7.8 (12H, m), 8.06 (1H, d,  $J = 8\text{Hz}$ )  
 Mass: 370 ( $M^+ + H$ )

#### Example 48

- 10 The following compounds are prepared in a similar manner to those of Preparation 31, Example 42, Example 43, Example 44 and Example 25.

- (1) 2-{3-[(1H-benzimidazol-2-ylmethyl)amino]propyl}-4(3H)-quinazolinone  
 dihydrochloride  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 2.2-2.9 (4H, m), 4.72 (2H, s), 7.2-7.8 (6H, m),  
 15 8.0-8.2 (2H, m), 8.2-8.3 (1H, m)  
 Mass: 334 ( $M^+ + H$ )

#### Example 49

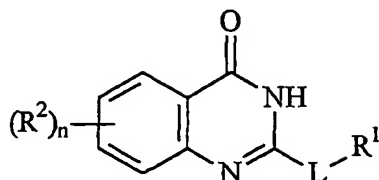
- The following compounds are prepared in a similar manner to that of Preparation 20 31, Example 42, Example 43 and Example 44.

- (1) 2-[3-(diethylamino)propyl]-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 0.94 (6H, t,  $J = 7.4\text{Hz}$ ), 1.8-2.0 (2H, m), 2.3-2.7 (8H, m), 7.44 (1H, t,  $J = 8.2\text{Hz}$ ), 7.57 (1H, d,  $J = 8.2\text{Hz}$ ), 7.76 (1H, d,  $J = 8.2\text{Hz}$ ), 8.06 (1H, d,  $J = 8.2\text{Hz}$ )  
 25 Mass: 260 ( $M^+ + H$ )
- (2) 2-[3-(2,3-dihydro-1H-inden-2-ylamino)propyl]-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.8-2.0 (2H, m), 2.4-3.0 (9H, m), 6.8-8.0 (8H, m)
- (3) 2-[3-(2,3-dihydro-1H-inden-2-ylamino)propyl]-8-methyl-4(3H)-quinazolinone  
 30  $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.8-2.0 (2H, m), 2.51 (3H, s), 2.6-2.8 (4H, m), 7.1-7.3 (4H, m), 7.29 (1H, t,  $J = 8\text{Hz}$ ), 7.62 (1H, d,  $J = 8\text{Hz}$ ), 7.91 (1H, d,  $J = 8\text{Hz}$ )  
 Mass: 334 ( $M^+ + H$ )
- (4) 2-{3-[2,3-dihydro-1H-inden-2-yl(methyl)amino]propyl}-4(3H)-quinazolinone  
 $^1\text{H}$  NMR (200MHz, DMSO- $d_6$ ,  $\delta$ ): 1.8-2.0 (2H, m), 2.18 (3H, s), 2.2-3.3 (9H, m),  
 35 7.0-7.2 (4H, m), 7.38 (1H, t,  $J = 8\text{Hz}$ ), 7.58 (1H, d,  $J = 8\text{Hz}$ ), 7.78 (1H, t,  $J = 8\text{Hz}$ ), 8.05 (1H, d,  $J = 8\text{Hz}$ )

## CLAIMS

1. A compound of the formula:

5



- 10 wherein  $R^1$  is optionally substituted cyclic amino groups or optionally substituted amino group,  
 $R^2$  is substituent,  
 $n$  means an integer from 0 to 4, and  
 $L$  is lower alkylene or lower alkenylene,  
 15 or its prodrug, or their salts.
2. The compound according to claim 1, wherein  
 $R^2$  is halogen, nitro, amino, acylamino, aryl(lower)alkylamino, lower alkylamino,  
 lower alkyl, lower alkynyl, lower alkoxy, acyl, or cyclic amino group optionally  
 20 substituted with lower alkyl.
3. The compound according to claim 2, wherein  
 $R^1$  is (1) cyclic amino group optionally substituted with one or more substituent(s)  
 selected from the group consisting of halogen, cyano, hydroxy, amino, oxo, lower  
 25 alkyl, lower alkenyl, lower alkynyl, aryl(lower)alkyl, aryl(lower)alkynyl, acyl, lower  
 alkylsulfonyl, optionally substituted heteroaryl and optionally substituted aryl, or (2)  
 amino optionally substituted with 1 or 2 substituent(s) selected from the group  
 consisting of lower alkyl, aryl, heteroaryl(lower)alkyl, aryl(lower)alkoxycarbonyl and  
 aryl(lower)alkyl optionally substituted with aryl or aryloxy.  
 30
4. The compound according to claim 3, wherein  
 $R^1$  is cyclic amino group optionally substituted with optionally substituted heteroaryl  
 or optionally substituted aryl.
- 35 5. The compound according to claim 4, wherein  
 $R^1$  is cyclic amino group with saturated or unsaturated monocyclic group with one or

more nitrogen atom(s), which is substituted with optionally substituted heteroaryl or optionally substituted aryl.

6. The compound according to claim 5, wherein
  - 5  $R^1$  is tetrahydropyridyl, piperidyl or piperazinyl, each of which is substituted with optionally substituted heteroaryl or optionally substituted aryl:
7. The compound according to any one of claims 4, 5 and 6, wherein
  - 10 substituent(s) of optionally substituted heteroaryl is lower alkyl, halogen, cyano or acyl, or
  - substituent(s) of optionally substituted aryl is halogen, cyano, hydroxy, carboxy, nitro, amino, lower alkyl, hydroxy(lower)alkyl, lower alkoxy, lower alkylthio, halo(lower)alkyl, lower alkylamino, acylamino, halo(lower)alkoxy, aryl, aryloxy, or acyl.
  - 15
8. The compound according to claim 3, wherein
  - $R^1$  is cyclic amino groups with saturated and unsaturated fused cyclic groups, which is substituted with optionally substituted lower alkyl.
9. The compound according to any one of claims 4, 5, 6, 7 and 8, wherein
  - 20 L is trimethylene.
10. The compound according to claim 9, which is selected from the group consisting of:
  - 25 (1) 5-chloro-2-[3-(4-phenyl-3,6-dihydro-1(2H)-pyridinyl)propyl]-4(3H)-quinazolinone,
  - (2) 2-{3-[4-(4-hydroxyphenyl)-3,6-dihydropyridin-1(2H)-yl]propyl}-4(3H)-quinazolinone,
  - (3) 8-methyl-2-{3-[4-(4-methoxyphenyl)-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone,
  - 30 (4) 8-chloro-2-{3-[4-(4-fluorophenyl)-3,6-dihydro-1(2H)-pyridinyl]propyl}-4(3H)-quinazolinone,
  - (5) 8-chloro-2-{(1E)-3-[4-(4-fluorophenyl)-3,6-dihydro-1(2H)-pyridinyl]-1-propenyl}-4(3H)-quinazolinone,
  - (6) 8-Chloro-2-{[4-(4-pyridinyl)-3,6-dihydro-1(2H)-pyridinyl] propyl}-4(3H)-quinazolinone,
  - 35 (7) 2-{3-[4-(4-chlorophenyl)-1-piperazinyl]propyl}-4(3H)-quinazolinone,



(8) 2-{3-[4-(4-pyridyl)-1-piperazinyl]propyl}-4(3H)-quinazolinone,

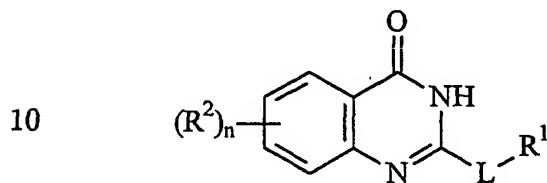
(9) 2-[3-(1,4,5,6-Tetrahydrobenzo[f]isoquinolin-3(2H)-yl)propyl]-

4(3H)-quinazolinone, and

(10) 8-methyl-2-[3-(1,3,4,9-tetrahydro-2H-pyrido[3,4-b]indol-2-yl)propyl]-

4(3H)-quinazolinone.

11. A process for preparing a compound of the formula:



wherein  $R^1$  is optionally substituted cyclic amino groups or optionally substituted amino group,

$R^2$  is substituent,

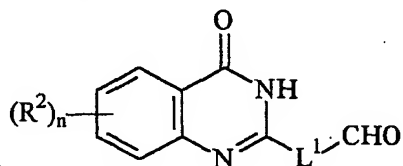
$n$  means an integer from 0 to 4, and

$L$  is lower alkylene or lower alkenylene,

or its prodrug, or their salts,

which comprises,

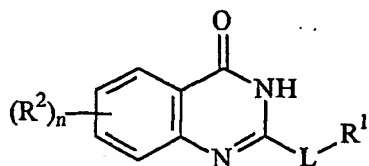
(1) reacting the formyl group of the compound (II) of the formula:



or its amination derivative, or their salt, and imino group of the compound (IV) of the formula:



or its salt, in the presence of a reducing agent to provide a compound of the formula:

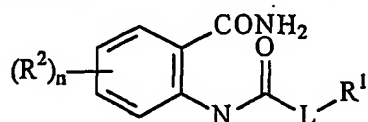


or its salt, in the above formulae,

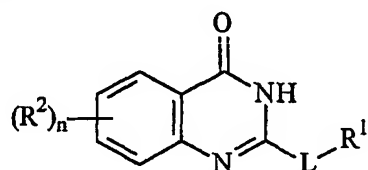
$R^1$ ,  $R^2$ ,  $n$  and  $L$  are each as defined above, and  $L^1$  is lower alkylene or lower

alkenylene delating a methylene group from the end of the one defined in L, or

(2) subjecting the compound (III) of the following formula:



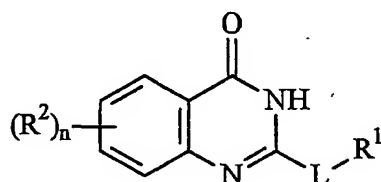
or its salt, to cyclization reaction in the presence of base to provide a compound of the formula:



or its salt, in the above formulae,

$R^1$ ,  $R^2$ ,  $n$  and  $L$  are each as defined above.

15 12. A pharmaceutically composition comprising a compound of the formula:



wherein  $R^1$  is optionally substituted cyclic amino groups or optionally substituted amino group,

$R^2$  is substituent,

25  $n$  means an integer from 0 to 4, and

$L$  is lower alkylene or lower alkenylene,

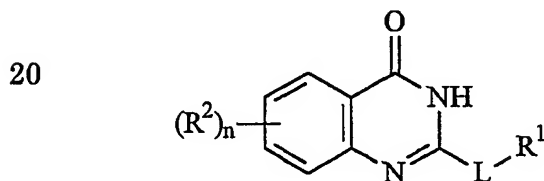
or its prodrug, or their pharmaceutically acceptable salts, and a pharmaceutically acceptable carrier, wherein said compound is present in an amount effective for inhibiting PARP activity.

30

13. The pharmaceutical composition of claim 12 for treating or preventing diseases ascribed by NMDA- and NO-induced toxicity.

35 14. The pharmaceutical composition of claim 12 for extending the lifespan or proliferative capacity of cells or altering gene expression of senescent cells

15. The pharmaceutical composition of claim 13 for treating or preventing tissue damage resulting from cell damage or death due to necrosis or apoptosis; neural tissue damage resulting from ischemia and reperfusion injury, neurological disorders and neurodegenerative diseases; neurodegenerative diseases; head trauma; stroke;
- 5 Alzheimer's disease; Parkinson's disease; epilepsy; Amyotrophic Lateral Sclerosis (ALS); Huntington's disease; schizophrenia; chronic pain; ischemia and loss following hypoxia; hypoglycemia; ischemia; trauma; nervous insult; previously ischemic heart or skeletal muscle tissue; radiosensitizing hypoxic tumor cells; tumor cells from recovering from potentially lethal damage of DNA after radiation therapy;
- 10 skin aging; atherosclerosis; osteoarthritis; osteoporosis; muscular dystrophy; degenerative diseases of skeletal muscle involving replicative senescence; age-related macular degeneration; immune senescence; AIDS; and other immune senescence diseases; inflammatory bowel disorders (e.g., colitis); arthritis; diabetes; endotoxic shock; septic shock; and tumor.
- 15
16. A method of inhibiting PARP activity comprising administering a compound of the formula:



- wherein R<sup>1</sup> is optionally substituted cyclic amino groups or optionally substituted amino group,
- 25 R<sup>2</sup> is substituent,
- n means an integer from 0 to 4, and
- L is lower alkylene or lower alkenylene,
- or its prodrug, or their pharmaceutically acceptable salts, and a pharmaceutically acceptable carrier, wherein said compound is present in an amount effective for
- 30 inhibiting PARP activity.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/10601

## A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D239/90 C07D401/06 C07D471/04 C07D417/14 C07D401/14  
 C07D409/14 C07D403/06 A61K31/517 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EP0-Internal

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | GB 1 331 522 A (BYK GULDEN LOMBERG<br>CHEMISCHE FABRIK)<br>26 September 1973 (1973-09-26)<br>the whole document  | 1, 12, 15             |
| X          | SAARI W S ET AL: "SYNTHESIS AND<br>EVALUATION OF 2-PYRIDINONE DERIVATIVES AS<br>HIV-1- SPECIFIC REVERSE TRANSCRIPTASE<br>INHIBITORS.2.ANALOGUES OF<br>3-AMINOPYRIDIN-2(1H)-ONE"<br>JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN<br>CHEMICAL SOCIETY. WASHINGTON, US,<br>vol. 35, no. 21,<br>16 October 1992 (1992-10-16), pages<br>3792-3802, XP000572378<br>ISSN: 0022-2623<br>table I, compound 15 | 1, 12, 15             |



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

## \* Special categories of cited documents:

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the international filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the international search

23 April 2002

Date of mailing of the international search report

10/05/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2  
 NL - 2280 HV Rijswijk  
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,  
 Fax: (+31-70) 340-3016

Authorized officer

Beslier, L

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/JP 01/10601

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| X          | WO 94 07869 A (ZENECA LTD.)<br>14 April 1994 (1994-04-14) .<br>claims 1-10<br>----   | 1, 12, 15             |
| A          | CHEMICAL ABSTRACTS, vol. 99, no. 13,<br>26 September 1983 (1983-09-26)<br>Columbus, Ohio, US;<br>abstract no. 98829,<br>AHMED, H. M. S.: "Studies on some<br>pharmacological properties of certain<br>2,3-disubstituted 4(3H)-quinazolinone<br>derivatives"<br>XP002197144<br>abstract<br>& BULL. FAC. PHARM. (CAIRO UNIV.) (1982),<br>VOLUME DATE 1980, 19(1), 11-21 ,<br>1982,<br>---- | 1-16                  |
| A          | WO 98 33802 A (NEWCASTLE UNIVERSITY<br>VENTURES LTD.) 6 August 1998 (1998-08-06)<br>cited in the application<br>the whole document<br>----   | 1-16                  |
| A          | WO 95 24379 A (CANCER RESEARCH CAMPAIGN<br>TECHNOLOGY LTD.)<br>14 September 1995 (1995-09-14)<br>cited in the application<br>the whole document<br>----  | 1-16                  |
| A          | WO 99 11624 A (GUILFORD PHARMACEUTICALS )<br>11 March 1999 (1999-03-11)<br>cited in the application<br>the whole document<br>-----   | 1-16                  |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 01/10601

| Patent document<br>cited in search report |   | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---|---------------------|----------------------------|---------------------|
| GB 1331522                                | A | 26-09-1973          | DE 2027645 A1              | 09-12-1971          |
|   |   |                     | AT 318628 B                | 11-11-1974          |
|   |   |                     | AT 317899 B                | 25-09-1974          |
|   |   |                     | AT 318615 B                | 11-11-1974          |
|   |   |                     | BE 768137 A1               | 06-12-1971          |
|   |   |                     | CA 951319 A1               | 16-07-1974          |
|   |   |                     | CH 558374 A                | 31-01-1975          |
|   |   |                     | CH 569732 A5               | 28-11-1975          |
|   |   |                     | CH 557829 A                | 15-01-1975          |
|   |   |                     | FR 2100726 A5              | 24-03-1972          |
|   |   |                     | LU 63267 A1                | 23-08-1972          |
|   |   |                     | NL 7107695 A               | 07-12-1971          |
|   |   |                     | US 3984555 A               | 05-10-1976          |
|   |   |                     |                            |                     |
| WO 9407869                                | A | 14-04-1994          | AU 4829793 A               | 26-04-1994          |
|   |   |                     | WO 9407869 A1              | 14-04-1994          |
|   |   |                     | GB 2271111 A               | 06-04-1994          |
|   |   |                     | MX 9306034 A1              | 30-06-1994          |
|   |   |                     | ZA 9306768 A               | 30-03-1994          |
| WO 9833802                                | A | 06-08-1998          | AU 5873998 A               | 25-08-1998          |
|   |   |                     | EP 0966476 A1              | 29-12-1999          |
|   |   |                     | WO 9833802 A1              | 06-08-1998          |
|   |   |                     | JP 2001511776 T            | 14-08-2001          |
|   |   |                     | US 6156739 A               | 05-12-2000          |
| WO 9524379                                | A | 14-09-1995          | AT 184271 T                | 15-09-1999          |
|   |   |                     | AT 210651 T                | 15-12-2001          |
|   |   |                     | AU 693167 B2               | 25-06-1998          |
|   |   |                     | AU 1856595 A               | 25-09-1995          |
|   |   |                     | CA 2184747 A1              | 14-09-1995          |
|   |   |                     | CN 1143358 A , B           | 19-02-1997          |
|   |   |                     | DE 69512036 D1             | 14-10-1999          |
|   |   |                     | DE 69512036 T2             | 30-12-1999          |
|   |   |                     | DE 69524641 D1             | 24-01-2002          |
|   |   |                     | DK 749415 T3               | 20-03-2000          |
|   |   |                     | DK 879820 T3               | 02-04-2002          |
|   |   |                     | EP 0749415 A1              | 27-12-1996          |
|   |   |                     | EP 0879820 A1              | 25-11-1998          |
|   |   |                     | EP 0897915 A1              | 24-02-1999          |
|   |   |                     | ES 2135707 T3              | 01-11-1999          |
|   |   |                     | WO 9524379 A1              | 14-09-1995          |
|   |   |                     | GR 3031886 T3              | 29-02-2000          |
|   |   |                     | JP 9510704 T               | 28-10-1997          |
|   |   |                     | US 6015827 A               | 18-01-2000          |
|   |   |                     | US 6316455 B1              | 13-11-2001          |
|   |   |                     | US 5756510 A               | 26-05-1998          |
| WO 9911624                                | A | 11-03-1999          | US 2002022636 A1           | 21-02-2002          |
|   |   |                     | AU 9297898 A               | 22-03-1999          |
|   |   |                     | AU 9298098 A               | 22-03-1999          |
|   |   |                     | AU 9298198 A               | 22-03-1999          |
|   |   |                     | AU 9298698 A               | 22-03-1999          |
|   |   |                     | AU 9299198 A               | 22-03-1999          |
|   |   |                     | AU 9374898 A               | 22-03-1999          |
|   |   |                     | BR 9812428 A               | 26-09-2000          |
|   |   |                     | CN 1278797 T               | 03-01-2001          |
|   |   |                     | EP 1009739 A2              | 21-06-2000          |

# INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 01/10601

| Patent document<br>cited in search report | Publication<br>date | Patent family<br>member(s) | Publication<br>date |
|---|---------------------|----------------------------|---------------------|
| WO 9911624                                | A                   | EP 1012145 A1              | 28-06-2000          |
|   |                     | EP 1012153 A1              | 28-06-2000          |
|   |                     | HU 0004693 A2              | 28-10-2001          |
|   |                     | NO 20001002 A              | 27-04-2000          |
|   |                     | PL 339082 A1               | 04-12-2000          |
|   |                     | TR 200001557 T2            | 22-01-2001          |
|   |                     | WO 9911623 A1              | 11-03-1999          |
|   |                     | WO 9911649 A2              | 11-03-1999          |
|   |                     | WO 9911622 A1              | 11-03-1999          |
|   |                     | WO 9911644 A1              | 11-03-1999          |
|   |                     | WO 9911624 A1              | 11-03-1999          |
|   |                     | WO 9911628 A1              | 11-03-1999          |
|   |                     | US 6197785 B1              | 06-03-2001          |
|   |                     | US 2002028813 A1           | 07-03-2002          |
|   |                     | US 6121278 A               | 19-09-2000          |
|   |                     | US 6235748 B1              | 22-05-2001          |
|   |                     | ZA 9808010 A               | 03-03-1999          |
|   |                     | ZA 9808011 A               | 03-03-1999          |
|   |                     | ZA 9808012 A               | 03-03-1999          |
|   |                     | ZA 9808013 A               | 03-03-1999          |
|   |                     | ZA 9808015 A               | 03-03-1999          |